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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION THIS OPINION RELATES TO: ALL ACTIONS	MDL No. 2243 Civil Action No. 3:08-08 (FLW) **OPINION**

WOLFSON, Chief Judge:

In this failure-to-warn case, more than 500 individuals ("Plaintiffs") who took Fosamax, a drug manufactured by Defendant Merck Sharp & Dohme ("Defendant" or "Merck") to prevent and treat osteoporosis in postmenopausal women, brought suit claiming that they suffered atypical femoral fractures between 1999 and 2010. More than eight years ago, following a bellwether trial, the late Hon. Joel A. Pisano, U.S.D.J., granted summary judgment in favor of Merck, ruling that federal law preempted Plaintiff's state law failure-to-warn claims.[1] *In re Fosamax (Alendronate Sodium) Prod. Liab. Litig.*, 951 F. Supp. 3d 695, 701, 703-04 (D.N.J. 2013) [hereinafter *Glynn*]. On appeal, the Third Circuit vacated and remanded this matter, concluding that preemption presented "a question of fact for the jury," not a question of law for the judge. *In re Fosamax (Alendronate Sodium) Prod. Liab. Litig.*, 852 F. 3d 268, 271, 293 (3d Cir. 2017) [hereinafter *Fosamax*], *vacated and remanded*, 139 S.Ct. 1668. And, in answering that question, the Third Circuit held that the jury

[1] After Judge Pisano retired from the Court, the Multidistrict Litigation Panel reassigned this MDL to me.

must apply a heightened standard of proof, sustaining the preemption defense only if Merck proved it by "clear and convincing evidence." *Id.* at 285-86. Merck, however, petitioned for a writ of certiorari, which was granted by the United States Supreme Court. In *Merck Sharpe & Dohme Corp. v. Albrecht*, 139 S.Ct. 1668, 1676, 1679-80 (2019), the Supreme Court vacated and remanded the Third Circuit's decision, holding that the preemption inquiry is "a legal one for the judge, not a jury." Upon remand, the Third Circuit returned the case to this Court to decide "in the first instance whether the plaintiffs' state law claims are preempted by federal law under the standards described by the Supreme Court." Order at 1, No. 14-1900 (3d Cir. Nov. 25, 2019). The Third Circuit further instructed this Court "to determine the effect of the [Food and Drug Administration's ("FDA" or "Agency")] Complete Response Letter [("CRL")] and other communications with Merck on the issue of whether such agency actions are sufficient to give rise to preemption." *Id.*

On remand, Merck reiterates its position that federal law preempts Plaintiffs' state law failure-to-warn claims. In particular, Defendant relies on the FDA's 2019 communication, in the form of a CRL, rejecting a warning concerning atypical femoral fractures that Merck proposed. Plaintiffs, on the other hand, argue that the CRL is not "clear evidence" that the FDA would have rejected any and all warnings. Having reviewed the submission of the parties, the Court finds that based on clear and convincing evidence, Defendant fully informed the FDA of the justifications for its proposed warning, which was adequate under state law and encompassed the injury Plaintiffs allege here, and the FDA, in turn, informed Defendant that it would not

approve changing the Fosamax label to include that warning in the CRL. Because the FDA's rejection was predicated on insufficient evidence of a causal link between Fosamax and atypical femoral fractures, it is clear that the Agency would not have approved a differently worded warning about such a risk. Plaintiffs' state law failure-to-warn claims are therefore preempted, and Defendant's Motion for Summary Judgment is **GRANTED**.

FACUAL BACKGROUND AND PROCEDURAL HISTORY

The factual background and procedural history of this case, which are largely not in dispute, are primarily adopted from the Supreme Court and Third Circuit's decisions in this matter, as well as Judge Pisano's dual decisions in *Glynn* and *In re Fosamax (Alendronate Sodium) Prod. Liab. Litig.*, 2014 WL 1266994, at *17 (D.N.J. Mar. 22, 2014) [hereinafter *OTSC Opinion*].

A. Fosamax

Merck manufactures Fosamax, a drug that treats and prevents osteoporosis in postmenopausal women. *Merck*, 139 S.Ct. at 1668. Fosamax belongs to a class of drugs called "bisphosphonates," which operate on the "remodeling process," where the body breaks down bones and builds them back up. In postmenopausal women, this process can "fall out of sync," *id.* at 1673, such that the body removes old bone cells faster than it replaces them. When resorption exceeds formation, the result is osteoporosis, or low bone mass that increases the risk of fractures. Fosamax "slows the breakdown of old bone cells and thereby helps postmenopausal women avoid [such] fractures." *Id.* However, by reducing resorption, the drug may cause

some microscopic stress fractures to develop into a specific type of stress fracture known as atypical femoral fractures, or complete breaks that "cause great pain and require surgical intervention to repair." *Id.* at 1674.

A low energy, or also known as atypical, fracture is defined as one that is caused by the equivalent of a fall from standing height or less, which involves minimal force. A stress fracture is defined as a partial or complete fracture occurring with either normal or increased activity, but without an identifiable external traumatic event. Stress fractures, in this context, are included in the larger group of low-energy fractures. In postmenopausal osteoporotic women, the proximal femur is one of the most commonly affected sites for fractures, as are the pelvis, distal tibia and metatarsals. *See* Def. Br., Ex. 1 at A2751-52.

B. The Regulatory Framework for Drug Labeling

Congress has charged the FDA with ensuring that every prescription drug on the market is "safe for use under the conditions prescribed, recommended, or suggested" in its "labeling." 21 U.S.C. § 355(d). As that directive suggests, labeling is the "centerpiece" of the FDA's risk management strategy for approved drugs, and the primary means by which the FDA communicates its conclusions about drug safety to the public. 71 Fed. Reg. 3922, 3944. Prospective drug manufacturers, such as Merck, must work with the FDA to develop an appropriate label when they submit a new drug for approval. 21 U.S.C. §§ 355(a), (b), (d)(7); 21 C.F.R. § 314.125(b)(6). The FDA

closely regulates the safety information on drug labels, down to the exact text of warnings.[2] 21 U.S.C. § 355(b)(1)(F); 21 C.F.R. § 201.57(a).

Drug labels include two sections relevant to this case: a "Precautions" section and an "Adverse Reactions" section. The Precautions section narrowly describes "clinically significant adverse reactions," including any that are "serious even if infrequent." 21 C.F.R. § 201.57(c)(6)(i). The Adverse Reactions section more broadly describes "the overall . . . profile of the drug based on the entire safety database," including a list of all "undesirable effect[s], reasonably associated with use." *Id.* § 201.57(c)(7).

The threshold for placing a warning regarding an adverse event in the Precautions section is "reasonable evidence of a causal association." 21 C.F.R. § 201.57(c)(6)(iii) (providing that the Precautions section "must be revised to include a warning about a clinically significant hazard as soon as there is [such evidence] . . . a causal relationship need not have been definitely established"); Fed. Reg. 49,603, 49,604. The FDA designed this standard so as not to dilute "more important warnings" or "deter appropriate use." 73 Fed. Reg. at 49,605, 40,606. In other words, the Precautions section is reserved for a "discrete set" of serious risks that would

2 In this context, the label "refers more broadly to the written material that is sent to the physician who prescribes the drug and . . . that comes with the prescription bottle when the drug is handed to the patient at the pharmacy." *Merck*, 139 S.Ct. at 1672; 21 U.S.C. § 321(m). The label contains detailed information about the drug's medical uses and health risks. 21 U.S.C. § 355(b)(1)(F); 21 C.F.R. § 201.57(a). The FDA regulates the content, format, and order of the safety information on the drug label. 21 C.F.R. § 201.57(c). Drug labels must include, *inter alia*, warnings and precautions about potential safety hazards and adverse reactions for which there is sufficient evidence of, as determined by the FDA, a causal relationship between the drug and the occurrence of the adverse event. *See infra*.

affect a doctor's prescribing decisions or be "potentially fatal." 71 Fed. Reg. 3922-01, 3946; FDA, Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, at 3 (Oct. 2011). On the other hand, the threshold for warning of an adverse event in the Adverse Reactions section is comparatively lower: "some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event." 21 C.F.R. § 201.57(c)(7).

New information about a drug may require changing its label. 21 U.S.C. §§ 314.80(c), 314.81(b)(2)(i). A drug manufacturer may change its label in one of two ways. More commonly, it may seek advance permission from the FDA through a Prior Approval Supplement Application ("PAS"). 21 C.F.R. § 314.70(b). Alternatively, it may change a label immediately and unilaterally through a Changes Being Effected Application ("CBE") to reflect "newly acquired information" about "evidence of a casual association between the drug and a risk of harm." *Merck*, 139 S.Ct. at 1673 (quotations omitted); 21 U.S.C. § 314.70(c)(6)(iii)(A); 21 C.F.R. § 314.3(b) (defining "[n]ewly acquired information" to mean, *inter alia*, risks not previously known or previously underestimated). Whatever method a manufacturer chooses, it must meet the causal thresholds described above, and significantly, the FDA retains authority to reject even a CBE amendment if there is insufficient evidence of a link between the drug and the adverse event. 73 Fed. Reg. 2848, 2851; 21 C.F.R. § 314.70(c)(6)(iii)(A) (providing that the FDA will approve a label change only if "the

evidence of a causal association satisfies the standard for inclusion in the labeling"); *id.* §§ 314.125(b)(6), (b)(8).

Because of the availability of the CBE process, "a drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." *Merck*, 139 S.Ct. at 1679. At the same time, the FDA will not approve a warning simply out of an abundance of caution whenever a manufacturer posits an association between a drug and an adverse event. As the FDA has long recognized, "[e]xaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug." 73 Fed. Reg. 2848, 2851. Because "labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance," the FDA prohibits "a change to labeling [, either through the PAS or CBE process,] to add a [Precautions] warning in the absence of [at least] reasonable evidence of an association." *Id.* This represents a more conservative approach than state tort law, which generally incentivizes a manufacturer to warn about every conceivable hazard to limit liability. *See Wyeth v. Levine*, 555 U.S. 555, 557 (2009).

Finally, the FDA has an independent obligation to ensure that drug labels reflect new risks. 21 U.S.C. § 355(o)(4)(A) (providing that, if the agency "becomes aware of new information, including any new safety information," which "should be included in the labeling of the drug," it "shall promptly notify the [manufacturer]"). Indeed, Congress has "reaffirmed the manufacturer's . . . ultimate responsibility for its label," including when it "granted the FDA th[e] authority" to mandate label

changes in 2007.[3] *Wyeth*, 555 U.S. at 571; 21 U.S.C. § 355(o)(4)(I). If new safety information arises regarding a particular risk, the manufacturer, similarly, maintains "a duty to provide a warning that adequately describe[s] that risk," *Wyeth*, 555 U.S. at 571, and "bears responsibility for the content of its label at all times," *Merck*, 139 S.Ct. at 1677 (explaining that this has "remained a central premise of federal drug regulation"), regardless of whether the FDA takes parallel action.

C. The Fosamax Label History

When the FDA approved Fosamax in 1995, the label did not warn of a risk of the adverse event Plaintiffs allege here, *i.e.*, atypical femoral fractures. *Fosamax*, 852 F. 3d at 271, 274-75. However, Merck was "aware of at least a theoretical risk" of such particular fractures as early as 1992, during clinical trials, and brought it to the FDA's attention at that time. *Merck*, 139 S. Ct. at 1674 (informing the FDA that "antiresorptive agents may inhibit microdamage repair by preventing . . . bone resorption at the sites of microdamage"). More evidence came to light after 1995, when "Merck began receiving adverse event reports from the medical community

3 FDA regulations also require a New Drug Application ("NDA") to disclose all "pertinent" safety information. 21 C.F.R. § 314.50 (requiring "reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source"); *id.* § 314.50(d)(5)(vi)(a) (requiring "an integrated summary of all available information about the safety of the drug product, including pertinent animal data[and] demonstrated or potential adverse effects of the drug"); *id.* § 312.50 (stating that "[s]ponsors are responsible for . . . providing [investigators] with the information they need to conduct an investigation properly . . . and ensuring that [the] FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug"). The FDA approval process is "onerous and lengthy." *Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472, 476 (2013).

indicating that long-term Fosamax users were suffering atypical femoral fractures."[4] *Merck*, 139 S.Ct. at 1674. Based on its own analysis of these increasing reports, in 2005, Merck preliminarily concluded that there was a statistically significant increase in the incidence of atypical femoral fractures among Fosamax users. Pl. Br., Ex. 8, at A1272-73.

Merck also "began to see numerous scholarly articles and case studies documenting possible connections between long-term Fosamax use and atypical femoral fractures." *Merck*, 139 S.Ct. at 1674. However, none of these studies concluded that Fosamax actually caused atypical femoral fractures, or even that they were definitively associated with Fosamax use. *Fosamax*, 852 F.3d at 275 (citing A1258) (stating that Fosamax may potentially increase the risk of such fractures); *id.* (citing A1237) (stating that Fosamax may be associated with such fractures; *id.* (citing A1243) (stating that certain findings raised the possibility that Fosamax may lead to such fractures). Still, Merck forwarded them to the FDA. *Fosamax*, 862 F.3d at 275.

In March 2008, Merck submitted to the FDA a 165-page periodic safety update, the twenty-ninth of its kind, with thirty pages dedicated to "recent publications" "implicat[ing] a link between prolonged bisphosphonate therapy and atypical low-energy non-vertebral fractures," and "relat[ing] these findings to severely suppressed bone turnover that may develop during long-term" use of Fosamax. Def. Rep. Br., Ex.

4 For example, in 2002, Merck received a report from a doctor who said that his hospital called atypical femoral fractures the "Fosamax Fracture" because "100% of patients in his practice who have experienced femoral fractures (without being hit by a taxicab), were taking Fosamax . . . for over 5 years." *Merck*, 139 S.Ct. at 1674 (quotations and citations omitted).

14, at A2597. Later that month, Merck sent the FDA a letter from the New England Journal of Medicine describing "a potential link between [bisphosphonate] use and low-energy fractures of the femur." *Id.*, Ex. 13. The FDA, in turn, informed Merck in June 2008, that it was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates" and was "concerned about this developing safety signal." Pl. Br., Ex. 10, at A1145. The Agency asked Merck for additional data and investigations by July 2008, and Merck complied.

In September 2008, while its data was pending review, Merck submitted to the FDA a PAS, *i.e.*, application to enlarge the warning label, to amend the Adverse Reactions section of the Fosamax label with a warning about "low-energy femoral shaft fractures," *id.*, Ex. 38, at A1349, and to cross-reference a longer discussion in the Precautions section. *Merck*, 139 S.Ct. at 1674. Specifically, Merck proposed adding the following language to the Precautions section:

> **Low-Energy Femoral Shaft Fracture**
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be

> considered, pending evaluation of the patient, based on individual benefit/risk assessment.

Pl. Br., Ex. 38 at A1371.[5]

As part of its PAS to the FDA, Merck submitted a lengthy analysis of femoral fractures in Fosamax users, cited to nine articles on such cases, and summarized the findings in a clinical overview. Merck opined that, although "[i]t is not possible with the present data to establish whether" Fosamax "increases the risk of . . . low-energy subtrochanteric and/or proximal shaft fractures," because they tended to arise alongside Fosamax use, it is "important to include an appropriate statement" about them in the drug's precautions section. *Id.*, Ex. 38, at A1349-51.

In April 2009, Merck discussed its pending PAS with FDA official, Dr. Scott Monroe. According to Merck's notes, Dr. Monroe expressed that, while the FDA could agree to additional language in the Adverse Reactions section, it likely would not approve similar language in the Precautions section. Pl. Br., Ex. 33, at A1970-71. Dr. Monroe advised that the FDA would likely "approach the issue of a precaution from the [perspective] of all bisphosphonates [from various drug manufacturers]" and was "working with the Office of Safety and Epidemiology ["OSE"] to do so." *Id.* But, because "the conflicting nature of the literature does not provide a clear path forward,

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[5] Based on a review of scientific studies in the record, including the FDA's September 2010 Task Force Report, as mentioned *supra*, I note that "low-energy femoral shaft fractures" are the same as "atypical femoral fractures." *See* Pl. Br., Ex. 2, at A1152. In layman's terms, "atypical femoral fractures" are a "rare type of complete, low-energy fracture [that] affects the thigh bone." *Merck*, 139 S.Ct. 1674. The low-energy component, critical to both terms, generally means that the fracture was caused by a slip, trip, or fall from standing height or less. *See* Pl. Br., Ex. 2. At A1152. Thus, low-energy fractures are typically caused by mechanical forces that would not ordinarily result in fracture, while high-energy fractures, on the other hand, are generally associated with a more focused and substantial trauma.

. . . more time will be need[ed] for FDA to formulate a formal opinion on the issue of a precaution." *Id.* In Dr. Monroe's view, Merck's "elevation" of the warning to a Precaution was "prolonging" approval of any amendment to the label. *Id.*

Later that month, an FDA official emailed Merck that the FDA was not prepared to include language about low-energy femoral fractures in the Precautions section, and "could . . . only" "approve[]" such a warning "in the adverse events section of the label." Def. Br., Ex. 3, at A1498. The official asked Merck to "hold off on the [Precautions] language" so that drug evaluators could "work with [the Office of Surveillance and Epidemiology] and Merck to decide on . . . atypical fracture language, if it is warranted." *Id.* The next month, in May 2009, officially responding to Merck's PAS, Dr. Monroe drafted a CRL which stated that the FDA approved a warning in the Adverse Reactions section, subject to some rewording, but rejected one in the Precautions section. Then, the FDA explained:

> We have completed the review of your [PAS], as amended, and have determined that we cannot approve these applications in their present form. We have described below our reasons for this action and our recommendation to address this issue.
>
> 1. While the Division agrees that atypical and subtrochanteric fractures should be added to the **ADVERSE REACTIONS, Post-Marketing Experience** subsections of the [Fosamax] labels, your justification for the proposed **PRECAUTIONS** section language is inadequate. Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting.

Def. Br., Ex. 2, at A1500-01.

On the same day that the FDA sent the CRL, Merck "asked the [Agency]" for a "teleconference to discuss what [Precautions language] may be acceptable." Pl. Br., Ex. 13. A few weeks later, undeterred, Merck again asked "for a meeting . . . to discuss the issues that were raised in the [CRL] to Merck's proposed text to the Precautions section." *Id.*, Ex. 14. Merck also asked to "leave the previous PAS active to permit further discussions with the agency." *Id.*, Ex. 15. The FDA "informed [Merck] that the proposal was not in-line with Dr. Monroe's request that all deficiencies need to be addressed to start a new review cycle," and any meeting must be formally requested. *Id.* Merck maintained that "[atypical] fractures should [still] be described in the Precautions section," and suggested "broach[ing]" that topic in an unrelated teleconference the following day, to which the FDA responded it might be "possible," albeit "not the objective of the meeting." *Id.*

Pursuant to FDA regulations, within one year of the CRL, Merck had to "resubmit" its application "addressing all deficiencies identified" in the CRL, withdraw it, or request a hearing, after which "the agency will either approve" or "refuse" the label change. 21 C.F.R. § 314.110(b). In July 2009, Merck elected to withdraw, Def. Br., Ex. 4, at A2961, change the Adverse Reactions section through a CBE amendment, as recommended by the FDA, *id.* at A2963-64, and leave the Precautions section as-is. But, Merck did not do so without reiterating, once more, its desire to add a Precautions warning. *Id.*

Unwavering, in March 2010, after reviewing the data submitted by Merck (and other manufacturers), the FDA issued a Drug Safety Announcement reiterating that

there was not yet "a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures." Def. Br., Ex. 5, at A1508-09. The FDA, however, announced that it would work with an outside Task Force, which included various experts in different agencies, to gather additional information. *Id.* In September 2010, the Task Force found that "there is evidence of a relationship between long-term [bisphosphonate] use and a specific type of subtrochanteric and femoral shaft fracture," although not enough to establish causation. Pl. Br., Ex. 2, at A1167. The FDA responded with another Drug Safety Announcement stating that, "[a]lthough it is not clear if bisphosphonates are the cause [of fractures], these unusual femur fractures have been identified in patients taking [such] drugs." Def. Br., Ex. 9, at A1512. The FDA then "assembled and [reviewed] all long term data available on the products, as well as all safety reports," and promised to "keep the public informed of additional findings." *Id.*

In October 2010, more than a year after the FDA sent Merck its CRL, the FDA, after completing its analysis, finally concluded that "atypical fractures may be related to long-term . . . bisphosphonate use," and announced that it would require all bisphosphonate manufacturers to add information on that risk to the Precautions sections of their labels. Pl. Br., Ex. 19, at A1118. In a media call accompanying the announcement, the FDA's Deputy Director of the Office of New Drugs stated that the Task Force Report made the Agency "confident" that atypical femur fractures are "potentially more closely related to" long-term use of bisphosphonates "than [we] previously had evidence for." Def. Br., Ex. 6, at A1396. The FDA wrote to Merck that

day to mandate a label change to Fosamax. Def. Br., Ex. 7, at A1516-17. Specifically, the FDA provided language for a warning in the Precautions section:

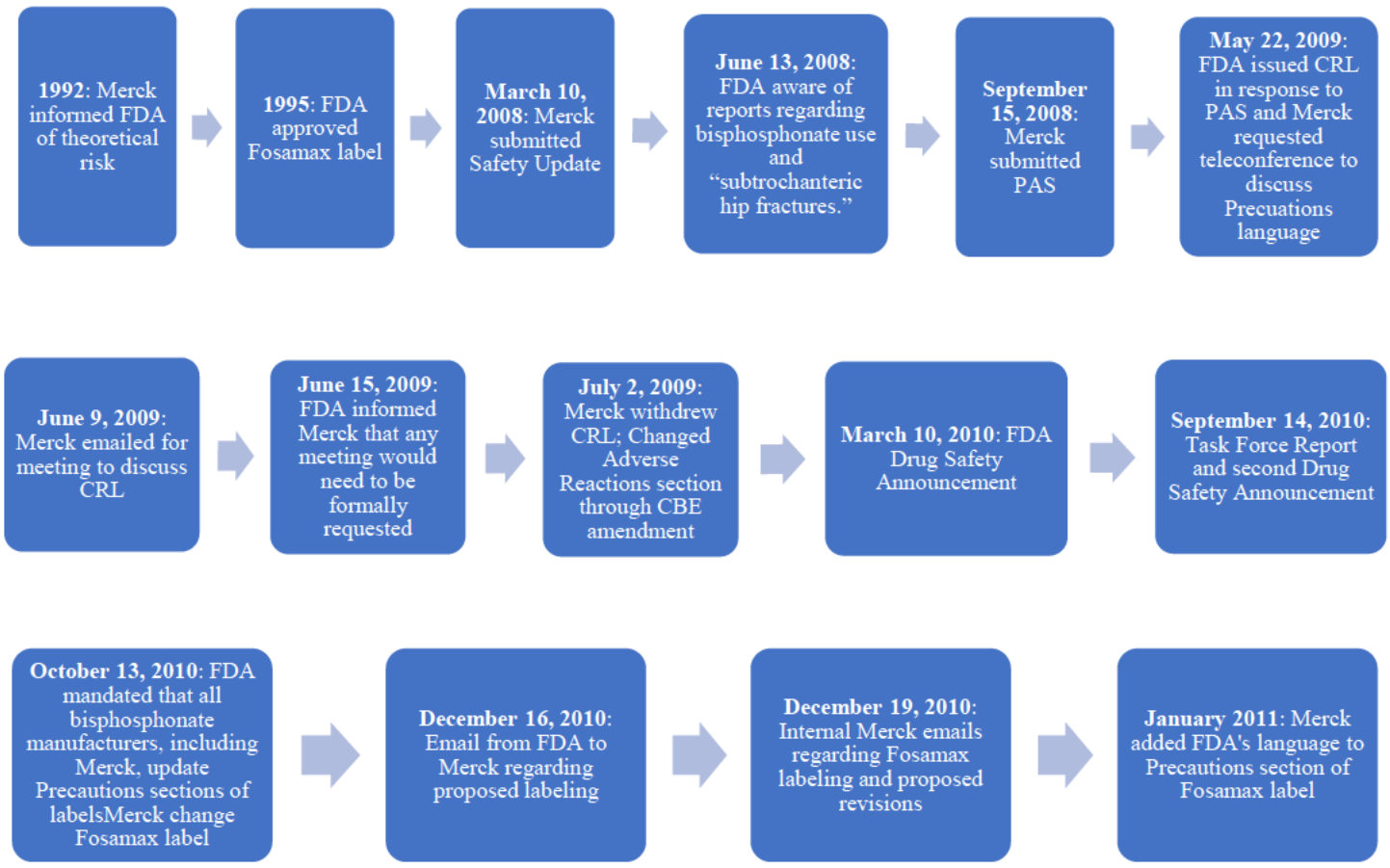
> **Atypical Subtrochanteric and Diaphyseal Femoral Fractures:**
>
> Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.
>
> Atypical femur fractures most commonly occur with minimal or no impact to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.
>
> Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out a femur fracture. Subjects presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Id.

In response, Defendant proposed revised language that, once again, referred to the risk of "stress fractures." Pl. Br., Ex. 21, at A1556-57. But, the FDA rejected that language, explaining that "the term 'stress fracture' was considered and was not accepted" because, "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use." *Id.* at A1540. In January 2011, Merck

added the FDA's language, nearly verbatim, to the Precautions section of the Fosamax label. *Id.*, Ex. 1, at A1070-71. That warning remains in place today.

Before discussing the case's procedural history, it is helpful to summarize the timeline of events:



D. The Parties' Prior Litigation

After the label change, Plaintiffs filed separate actions, in different states, seeking tort damages under state law. They claimed that, during the relevant period, Merck had a legal duty to warn them about the risk of atypical femoral fractures.

Merck argued, in response, that federal law preempted Plaintiffs' claims—specifically, the May 2009 CRL rejecting Merck's proposed label change.[6]

Following a bellwether trial, Judge Pisano agreed with Merck, and granted summary judgment in all cases. *OTSC Opinion*, 2014 WL 1266994, at *17 (D.N.J. Mar. 22, 2014); *Glynn*, 951 F. Supp. 3d at 701, 703-04. In particular, Judge Pisano found, "the fact that the FDA never required [Merck] to submit new language or change the label [after rejecting its proposed warning] demonstrates that the FDA did not think that the label should have been changed at that time," and there was "clear evidence that the FDA *would have* rejected a stronger Precautions warning because the FDA *did* reject a stronger Precautions warning." *OTSC Opinion*, 2014 WL 1266994, at *16 (emphasis in original). Indeed, Judge Pisano explained that pursuant to the Supreme Court's decision in *Wyeth*, a state law failure-to-warn claim is preempted if there is "clear evidence" that the FDA "would not have approved" any and all warnings.

Plaintiffs appealed the decision to the Third Circuit, which vacated Judge Pisano's decision. *Fosamax*, 852 F.3d 268. While recognizing that *Wyeth* controls the analysis, the Court of Appeals reasoned that "[t]he term 'clear evidence' . . . does not refer directly to the *type* of facts that a manufacturer must show, or to the circumstances in which preemption will be appropriate." *Id.* at 285. "Rather, it specifies how *difficult* it will be for the manufacturer to convince the factfinder that

6 In 2011, the Judicial Panel on Multidistrict Litigation consolidated these cases, which once exceeded 1,000 cases, for pre-trial administration in a multi-district litigation ("MDL") in the District of New Jersey. *In re: Fosamax (Alendronate Sodium) Prods. Liab. Litig. (No. II)*, 787 F. Supp. 2d 1355 (J.P.M.L. 2011).

the FDA would have rejected a proposed label change." *Id.* And, the court determined that the factfinder must be a jury not a judge. In that regard, the circuit court devised a novel standard: "for a defendant to establish a preemption defense under *Wyeth*, the [jury] must conclude that it is highly probable that the FDA would not have approved a change to the drug's label." *Id.* at 286.

Accepting Merck's petition for certiorari, the Supreme Court vacated the Third Circuit's opinion and judgment, holding that preemption must be decided by "a judge, not the jury," who, in turn, "must simply ask himself or herself whether the relevant federal and state laws irreconcilably conflict." *Merck*, 139 S.Ct. at 1676, 1679-80 (quotations and citation omitted). The Court also "elaborate[d] *Wyeth*'s" clear evidence standard "along the way." *Id.* It explained that "[c]lear evidence" exists where a drug manufacturer "show[s] that it fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." *Id.* at 1678. This will not "ordinarily" be the case. *Id.* at 1679. Moreover, "whatever the means the FDA uses to exercise its authority, those means must lie within the scope of the authority Congress has lawfully delegated," an "obvious point" which the Court reiterated even though "[t]he question of disapproval method is not now before [the Court]."[7] *Id.* at 1679-80.

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7 Justice Thomas wrote separately to explain his "understanding of the relevant pre-emption principles and how they apply to this case." *Merck*, 139 S.Ct. at 1681 (Thomas, J., concurring). Justice Thomas would not find preemption here because, in his view, nothing prevented Merck from using the CBE process to unilaterally add a warning to the Precautions section, even though the FDA retains the authority to reject a CBE amendment if it lacks causation. *Id.* at 1683. Further, according to Justice Thomas, even if Merck believed

The Supreme Court remanded to the Third Circuit with instructions "to consider fully the standards we have described." *Id.* at 1680-81. Rather than deciding the issue, the Third Circuit remanded to this Court "to determine in the first instance whether the plaintiffs' state law claims are preempted by federal law." Order at 1, No. 14-1900 (3d Cir. Nov. 25, 2019). The Third Circuit also instructed this Court "to determine the effect of the FDA's [CRL] and other communications with Merck on the issue of whether such agency actions are sufficient to give rise to preemption." *Id.*

E. The Parties' Arguments on Remand

The issue on remand is the same as it was eight years ago: whether the CRL "prohibited [Merck] from adding any and all warnings to the drug label that would satisfy state law." *Merck*, 139 S.Ct. at 1678. Plaintiffs answer in the negative, and advance several arguments, some of which merely restate their prior positions. First, they reiterate that Merck did not fully inform the FDA of the risks of Fosamax use. Pl. Br., at 30-35. Second, relying on Justice Thomas' concurrence, they argue for the

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that the FDA would have ultimately rejected a CBE amendment, that "hypothetical" would not constitute "[l]aw with pre-emptive effect," because "the possibility of impossibility is not enough." *Id.* Justice Thomas also rejected the preemptive effect of a CRL to the extent that such a letter is not a final agency action. *Id.* at 1682. In response, Justice Alito wrote separately to ensure that the Court's "discussion of the law and the facts" are not "misleading on remand." *Id.* at 1684 (Alito, J., concurring in the judgment). Chief Justice Roberts and Justice Kavanaugh joined his opinion. Justice Alito explained that "a statutory provision enacted after the events in [*Wyeth*] [ ] may have an important bearing" on this case, namely 21 U.S.C. § 355(o)(4)(A), which requires the FDA to initiate a label change under certain circumstances, but does not require it "to communicate to the relevant drug manufacturer that a label change is unwarranted; instead, the FDA could simply consider the new information and decide not to act." *Id.* Justice Alito then detailed the back and forth between Merck and the FDA to counter the majority's "one-sided account," stating "for years the FDA was: aware of this issue, communicating with drug manufacturers, studying all relevant information, and instructing healthcare professionals and patients alike to continue to use Fosamax as directed." *Id.* at 1685-86.

first time during this litigation that the CRL does not carry preemptive effect because it is not a final agency action, *id.* at 12-15, 27; however, they primarily dispute the meaning and scope of the CRL. They begin by arguing that Merck did not propose a warning that would have been adequate under state law in the first place. According to Plaintiffs, Merck's PAS emphasized "garden variety" stress fractures, which are scientifically different from the more serious atypical femoral fractures. *Id.* at 16-19, 24 n.4. Because of this focus, Plaintiffs posit that the FDA could not have rejected a warning about atypical femoral fractures at all, but only one about commonplace stress fractures. So construed, Plaintiffs advance that the CRL does not constitute "clear evidence" that the FDA would have prohibited any and all warnings to Fosamax, despite the Agency's other communications from the same time period. *Id.* at 24-30.

Merck maintains that it has always fully informed the FDA of the risks of Fosamax, particularly the risk of developing atypical femoral fractures. Def. Br., at 17-20; Def. Rep. Br., at 1-4. Merck also calls Plaintiffs' position that the CRL lacks preemptive power "idiosyncratic" and "unsupported" by law. Def. Br., at 28-30; Def. Rep. Br., at 11-12. Further, as to the meaning and scope of the CRL, Merck argues that its proposed warning was "perfectly" adequate under state law, *see* Def. Br., at 5-6, 14, 20-24, and the FDA rejected it for insufficient causal evidence linking bisphosphonate use to atypical femoral fractures, not because of the garden variety "stress fracture" language on which Plaintiffs improperly focus. Def. Br., at 23-27; Def. Rep. Br., at 10-11. As explained by Merck, to the extent that the basis for the

CRL was the FDA's skepticism of the underlying science regarding causal connection, there is necessarily clear evidence that the FDA would have rejected any and all changes to the Fosamax label. *See* 21 C.F.R. § 201.57(c)(6)(iii) (requiring "reasonable evidence of a causal association" to add a Precautions warning). Finally, even if the terms of the CRL themselves are unclear, Merck maintains that the letter constitutes clear evidence when construed in light of the FDA's other communications from around the same time. Def. Br., at 8-9, 21-23, 26; Def. Rep. Br., at 12-13, 15.

In short, Merck submits that the CRL conveyed that the FDA would not have approved any warning about atypical femoral fractures because of its then-existing perspective on the causal connection between such fractures and Fosamax use. Plaintiffs, on the other hand, take the position that the FDA had conveyed a far more limited message in the CRL: Merck's particular warning, as worded, was unacceptable, but the FDA might have approved different language had Merck proposed it through a revised PAS or a CBE amendment.

STANDARD OF REVIEW[8]

Summary judgment is appropriate "if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that

[8] While the parties' briefing does not discuss the legal standard the Court should apply on remand, they agreed that Rule 56 was the proper framework by which Judge Pisano resolved the dispositive issues presented by Defendant's preemption defense in the first instance. *Fosamax*, 852 F.3d at 281 ("Although both sides disputed the propriety of the show-cause procedure and the substance of Merck's preemption arguments, the parties and the District Court all agreed that Federal Rule of Civil Procedure 56 'provides the exclusive mechanism by which the Court can resolve the dispositive issues presented by Merck's preemption defense before trial(s).'"). Accordingly, because the Third Circuit remanded that very issue to me, I will apply that same standard, here.

there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed. R. Civ. P. 56(c). A factual dispute is genuine only if there is "a sufficient evidentiary basis on which a reasonable [factfinder] could find for the non-moving party," and it is material only if it has the ability to "affect the outcome of the suit under governing law." *Kaucher v. Cty. of Bucks*, 455 F.3d 418, 423 (3d Cir. 2006); *see also Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986). Disputes over irrelevant or unnecessary facts will not preclude a grant of summary judgment. *Anderson*, 477 U.S. at 248. "In considering a motion for summary judgment, a district court may not make credibility determinations or engage in any weighing of the evidence; instead, the non-moving party's evidence 'is to be believed and all justifiable inferences are to be drawn in his favor.'" *Marino v. Indus. Crating Co.*, 358 F.3d 241, 247 (3d Cir. 2004) (quoting *Anderson*, 477 U.S. at 255); *see also Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 587 (1986); *Curley v. Klem*, 298 F.3d 271, 276-77 (3d Cir. 2002).

The party moving for summary judgment has the initial burden of showing the basis for its motion. *Celotex Corp. v. Catrett*, 477 U.S. 317, 323 (1986). "If the moving party will bear the burden of persuasion at trial, that party must support its motion with credible evidence ... that would entitle it to a directed verdict if not controverted at trial." *Id.* at 331. On the other hand, if the burden of persuasion at trial would be on the nonmoving party, the party moving for summary judgment may satisfy Rule 56's burden of production by either (1) "submit[ting] affirmative evidence that negates an essential element of the nonmoving party's claim" or (2) demonstrating

"that the nonmoving party's evidence is insufficient to establish an essential element of the nonmoving party's claim." *Id.* Once the movant adequately supports its motion pursuant to Rule 56(c), the burden shifts to the nonmoving party to "go beyond the pleadings and by her own affidavits, or by the depositions, answers to interrogatories, and admissions on file, designate specific facts showing that there is a genuine issue for trial." *Id.* at 324; *see also Matsushita*, 475 U.S. at 586; *Ridgewood Bd. of Ed. v. Stokley*, 172 F.3d 238, 252 (3d Cir. 1999). In deciding the merits of a party's motion for summary judgment, the court's role is not to evaluate the evidence and decide the truth of the matter, but to determine whether there is a genuine issue for trial. *Anderson*, 477 U.S. at 249. Credibility determinations are the province of the factfinder. *Big Apple BMW, Inc. v. BMW of N. Am., Inc.*, 974 F.2d 1358, 1363 (3d Cir. 1992). There can be "no genuine issue as to any material fact," however, if a party fails "to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial." *Celotex*, 477 U.S. at 322-23. "[A] complete failure of proof concerning an essential element of the nonmoving party's case necessarily renders all other facts immaterial." *Id.* at 323; *Katz v. Aetna Cas. & Sur. Co.*, 972 F.2d 53, 55 (3d Cir. 1992).

DISCUSSION

I. Scope of Remand

The Third Circuit's mandate to this Court is clear: to determine whether Plaintiffs' state law failure-to-warn claims are preempted by federal law under the standards described by the Supreme Court in *Merck*. Order at 1, No. 14-1900 (3d

Cir. Nov. 25, 2019). In considering that question, the Third Circuit also instructed this Court to determine whether the FDA's CRL and other communications with Defendant are sufficient to give rise to preemption. *Id.*

As a preliminary matter, I note that on appeal, the Third Circuit vacated in full, Judge Pisano's underlying decision granting summary judgment in favor of Defendant, and the Supreme Court remanded with instructions to "consider fully" its elaboration of *Wyeth*'s clear evidence standard. Although I will conduct a *de novo* review of the legal issues and record, that does not necessarily mean, however, that Judge Pisano's factual findings will be ignored. In fact, my decision, here, will refer to Judge Pisano's opinion—at least as it relates to certain facts that are generally not in dispute. Indeed, Judge Pisano held a full trial on the merits, heard expert testimony, made numerous factual findings related to the narrow legal question on appeal in *Merck*, decided the preemption inquiry, and unsurprisingly, the evidence before me is virtually identical to the evidence presented then. To be certain, in 2013, Judge Pisano answered the preemption question posed to the Court on remand, here, consistent with the standard set forth in *Wyeth*—a standard that the Supreme Court did not overrule, but merely clarified and expounded upon in *Merck*. *See infra.* Indeed, *Merck* decided the narrow question of whether a jury or judge determines preemption—agreeing with Judge Pisano that it was a question for a judge. That issue constitutes new law, which I take as the law of this case now. *Bankers Trust Co. v. Bethlehem Steel Corp.*, 761 F.2d 943, 950 (3d Cir. 1985). But, what remains is exactly what Judge Pisano had to decide eight years ago: assess "in

the first instance" whether "the FDA would have rejected a change," considering any relevant factual disputes along the way. For these reasons, I will refer to Judge Pisano's factual findings where appropriate.

II. Preemption

"A fundamental principle of the Constitution is that Congress has the power to preempt state law." *Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 372 (2000). "Preemption follows automatically by the operation of the Supremacy Clause," *Wyeth*, 555 U.S. at 624 (Alito, J., concurring in the judgment), which "invalidates state laws that interfere with, or are contrary to, federal law." *Hillsborough County, Florida v. Automated Medical Laboratories, Inc.*, 471 U.S. 707, 712 (1985) (quotations omitted). Federal law can preempt state law in three ways: (1) express preemption, (2) field preemption, and (3) conflict preemption.[9] *Farina v. Nokia Inc.*, 625 F.3d 97, 115 (3d Cir. 2010). Both parties agree that the issue in this case is conflict preemption, which exists "where it is impossible for a private party to comply with both state and federal requirements." *Sprietsma v. Mercury Marine, a Div. of Brunswick Corp.*, 537 U.S. 51, 64 (2002) (quotations omitted); *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 620 (2011) ("The question . . . is whether the private party could independently do under federal law

[9] Federal regulations with the force of law preempt state laws in the same manner as federal statutes. *See, e.g.*, *Geier v. American Honda Motor Co.*, 529 U.S. 861 (2000); *Fellner v. Tri-Union Seafoods, L.L.C.*, 539 F.3d 237, 243 (3d Cir. 2008) ("Where Congress has delegated the authority to regulate a particular field to an administrative agency, the agency's regulations issued pursuant to that authority have no less preemptive effect than federal statutes, assuming those regulations are a valid exercise of the agency's delegated authority."). There is no dispute here that preemption, if appropriate, applies to all forms of state law, including civil actions based on state law, such as Plaintiffs' failure-to-warn claims. *Holk v. Snapple Beverage Corp.*, 575 F.3d 329, 331 (3d Cir. 2009).

what state law requires of it."); *Klotz v. Celentano Stadtmauer & Walentowicz LLP*, 991 F.3d 458, 463 (3d Cir. 2021).

Conflict, or impossibility, preemption "is a demanding defense" in the drug labeling context. *Wyeth*, 555 U.S. at 573. Essentially, a defendant must show that it could not have unilaterally changed its label in any way to add the warning required by state law. *Id.* at 569-71; *Sikkelee v. Precision Airmotive Corp.*, 822 F.3d 680, 703-704 (3d Cir. 2016); *Knight v. Boehringer Ingelheim Pharmaceuticals, Inc.*, 984 F.3d 329, 337 (4th Cir. 2021) ("A state law challenge to FDA-approved warnings, including a tort action under state law, can [ ] proceed only when the defendant had the unilateral ability to change that labeling; otherwise, the claim is preempted.").

The "possibility of impossibility [is] not enough" to establish preemption, *PLIVA*, 564 U.S. at 624 n.8 (quotations omitted); *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982) (rejecting "hypothetical" impossibility), and there is a "presumption against preemption," *Wyeth*, 555 U.S. at 595 n.3, which applies with special force in fields involving traditional state police powers. *Medtronic, Inc., v. Lohr*, 518 U.S. 470, 485 (1996) ("In all pre-emption cases, and particularly in those in which Congress has 'legislated . . . in a field which the States have traditionally occupied,' . . . [courts] 'start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress.'"). On the other hand, "the possibility of possibility" is not sufficient to *defeat* preemption. *PLIVA*, 564 U.S. at 624 n.8.

Rather, under *Wyeth*, if there is "clear evidence that the FDA would not have approved a change" to a drug's label, then it is impossible to comply with both federal and state law, and a plaintiff's failure-to-warn claims are preempted. 555 U.S. at 571. To establish clear evidence, a drug manufacturer must "show that it fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." *Merck*, 139 S.Ct. at 1678.

A. *Merck* Did Not Repudiate *Wyeth*[10]

At the outset, Plaintiffs contend that *Merck* repudiates *Wyeth*'s "premise that a manufacturer can show preemption by arguing that the FDA *would have* rejected a warning that it did not actually reject." Pl. Br., at 13-14 (emphasis in original). In Plaintiffs' view, impossibility preemption now "requires an affirmative showing that the FDA took 'action[]' to 'prohibit[] the drug manufacturer from adding any and all warnings to the drug label that would satisfy state law.'" Pl. Br., at 14 (quoting *Merck*, 139 S.Ct. at 1676, 1678).

Plaintiffs' position has some facial appeal, but it is ultimately specious. In *Wyeth*, the phrase "would not have approved" implies that a drug manufacturer may prove preemption without showing that it ever proposed or pursued a label change. Plaintiffs argue, however, that *Merck*'s phrasing of the law should be read to mean

10 In *Wyeth*, the Supreme Court rejected a drug manufacturer's preemption defense after an antinausea drug caused a patient to develop gangrene. Notably, there was no prior agency action in that case. The question was whether the FDA would have rejected a CBE amendment had the manufacturer attempted to pursue one. However, *Wyeth* does not instruct how this Court should interpret the meaning of an actual FDA decision on labeling, such as the CRL here that rejected Merck's proposed warning, which is the crux of this case.

that a manufacturer must have *actually requested* a label change that the FDA *then expressly rejected*.[11] Specifically, Plaintiffs rely exclusively on the Supreme Court's finding that to establish preemption, a manufacturer "is required to show that it fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." *Merck*, 139 S.Ct. at 1678. According to Plaintiffs, "anything less is insufficient." Pl. Br., at 14.

The Seventh Circuit has declined to view *Merck* in that manner, and I find that court's reasoning persuasive. *Dolin v. GlaxoSmithKline*, 951 F.3d 882, 890-91 (7th Cir. 2020). Indeed, the court, there, observed, in the context of a Rule 60(b) motion, that *Merck* "explicitly grounded its analysis in the Court's holdings in *Wyeth* . . . . began by citing the *Wyeth* 'clear evidence' standard[,] and formulated the question for decision in terms of the *Wyeth* framework," and further, that *Merck* uses "the language of ordinary evolution" rather than 'reversal and overruling." The Tenth Circuit ruled similarly. *Cerveny v. Aventis, Inc.*, 783 Fed. App'x. 804 n.8 (10th Cir. 2019) (dismissing, in the context of a Rule 28(j) letter, the contention that "only labeling changes sought by the manufacturer can lead to preemption.")

The Third Circuit also had an opportunity to reinterpret *Wyeth* in the manner proposed by Plaintiffs, but chose not do so in light of the facts before it. *In re Avandia*

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[11] Of course, this is precisely the factual scenario of this case; that is, Defendant claims that the CRL issued by the FDA expressly rejected Defendant's proposed warning regarding atypical femoral fractures. And, the primary dispute between the parties is whether the CRL could be so interpreted as to have rejected Defendant's proposed warning based on the causal connection between the use of Fosamax and atypical femoral fractures.

Marketing, Sales and Prod. Liab. Litig., 945 F.3d 749, 759 (3d Cir. 2019) (stating that it "need not speculate regarding the possibility that the FDA would have rejected the proposed warning" because the FDA in fact "*ordered*" one) (emphasis in original). In dozens of district court cases since, not one court has interpreted *Merck* to establish a new standard for impossibility preemption requiring actual agency or manufacturer action. *See, e.g.*, *In re Incretin-Based Therapies Prod. Liab. Litig.*, No. 13-2452, 2021 WL 880316 (S.D. Cal. Mar. 9, 2021) ("Plaintiffs also contend that [*Merck*] limited preemption to cases where the manufacturer has proposed a label change. The Court, however, does not read [*Merck*] so narrowly. Rather, the Court finds that [*Merck*] simply reiterated the lesson in *Wyeth* that the availability of the CBE label change process makes it such that a manufacturer will not 'ordinarily' be able to show an irreconcilable conflict between state and federal law."); *Crockett v. Luitpold Pharmaceuticals, Inc.*, No. 19-276, 2020 WL 433367, at *6 (E.D. Pa. Jan. 28, 2020) ("The defense of impossibility preemption is premised on a contention that a federal regulation would have prohibited the additional warnings that the plaintiff alleges state law requires."); *Yamagata v. Reckitt Benckiser LLC*, 445 F. Supp. 3d 28, 33 (N.D. Cal. 2020) ("The preemption analysis in [*Merck*] turned on whether the FDA would have approved a change to the drug label."); *McGrath v. Bayer HealthCare Pharmaceuticals, Inc.*, 393 F. Supp. 3d 161, 171 (E.D.N.Y. 2019) (finding preemption because the plaintiff "has not pleaded a plausible claim that the CBE regulation would have permitted [the defendant] to change the [drug] label"); *Silverstein v. Boehringer Ingelheim Pharmaceuticals, Inc.*, No. 19-81188, 2020 WL 6110909, at *9

(S.D. Fla. Oct. 7, 2020) ("[Preemption] can be satisfied [under *Merck*] even if the labeling change has not been presented to, and rejected by, the FDA.").

As such, based on these authorities, the "universal" standard that a manufacturer need not submit a PAS and CBE to the FDA to preserve its preemption defense remains intact after *Merck*. *See*, *e.g.*, *Cerveny v. Aventis, Inc.*, 155 F. Supp. 3d 1203, 1213-16 (D. Utah Mar. 16, 2016) ("Courts have universally rejected the notion that *Wyeth* requires a showing that the manufacturer attempted to apply the warning suggested by the plaintiff but that the labeling change was ultimately rejected by the FDA."); *In re Zofran (Ondansetron) Prod. Liab. Litig.*, No. 15-2657, 2021 WL 2209871, at *32 (D. Mass. June 1, 2021) ("Multiple courts have found [conflict] preemption where the manufacturer had not requested the precise warning sought by the plaintiffs when the FDA had nonetheless made it clear that it would not accept that label change."); *Ridings v. Maurice*, 444 F. Supp. 3d 973, 998 (W.D. Mo. 2020) (finding the second prong of *Merck* to be satisfied when all of the information justifying the proposed warning had been given to the FDA and the FDA did not revise the label to add the warning); *Seufert v. Merck Sharp & Dohme Corp.*, 187 F. Supp. 3d 1163, 1170 (S.D. Cal. May 11, 2016) ("[M]anufacturer submission of a proposed labeling change is relevant, but not dispositive, in determining whether a defendant can establish conflict preemption.").

In the end, it is, of course, the Supreme Court's "prerogative alone to overrule one of its precedents." *State Oil v. Khan*, 522 U.S. 3, 20 (1997). But it is difficult to reconcile the Court doing so when no party disputed *Wyeth*'s clear evidence standard

on appeal,[12] when the question before the Court was who should apply that standard, not whether the standard should survive, and when the Court itself held that its decision "flow[ed] *from* [its] precedents." 139 S.Ct. at 1678 (emphasis added). Accordingly, like all other courts having considered the issue, I find that *Merck* does not overrule *Wyeth*.

B. Prong One of Impossibility Preemption

I now turn to the substance of the parties' dispute. To establish impossibility preemption, a drug manufacturer must first show that it "fully informed the FDA of the justifications for the warning required by state law." *Merck*, 139 S.Ct. at 1678. I find that Defendant has met this standard; indeed, Judge Pisano found as much, the Third Circuit agreed, and the Supreme Court never questioned that finding on appeal. I reach the same conclusion based on my independent evaluation of the record.

After a full trial on the merits, including extensive expert testimony, Judge Pisano found no evidence that "Defendant failed to provide all the information it had . . . to the FDA." *Glynn*, 951 F. Supp. 2d at 703, 705. After a post-trial opportunity for Plaintiffs to present further proof, Judge Pisano again rejected their claim as "speculation." *OTSC Opinion*, 2014 WL 1266994, at *14, *17. The Third Circuit characterized the record in more certain terms: "Merck kept the FDA informed of the scores of case studies, reports, and articles . . . published documenting possible connections between long-term bisphosphonate use and atypical femoral fractures,"

12 Tellingly, Plaintiffs themselves argued on appeal that *Wyeth* "was correctly decided." U.S. Merits Brief, at *25-28.

and "[i]t is undisputed that the FDA was aware of the possible link between Fosamax and atypical fractures well before September 2010." *Fosamax*, 852 F.3d at 275, 296. The Supreme Court did not consider—let alone challenge—these factual findings on appeal. *Merck*, 139 S.Ct. at 1680.

Plaintiffs disagree, pointing first to the way in which the Supreme Court's summary of the facts characterizes what the FDA knew and when.[13] *See, e.g.*, *Merck*, 139 S.Ct. at 1673-76. But that is insufficient to support the inference that the Court *actually found* that Merck did not fully inform the FDA of the risks of Fosamax. For one, the Court is "an appellate tribunal, ill-equipped for the task of factfinding," and prong one of impossibility preemption is a fact-intensive inquiry involving a record exceeding one-thousand pages. *Ohio v. Wyandotte Chems. Corp.*, 401 U.S. 493, 498 (1971). More to the point, the Court does not "lightly overturn the concurrent findings of the two lower courts" on factual matters, in the background section of an opinion, especially not without any explanation, and when such findings were never on review

[13] Generally speaking, the Supreme Court used a harsher tone when describing Merck's actions throughout the labeling process. *Merck*, 139 S.Ct. at 1673-76. The Court stated that at the time the FDA first approved the Fosamax label in 1995, Merck scientists were aware of the risk of atypical femoral fractures, but "perhaps because [Merck's] concerns were only *theoretical*, the FDA approved Fosamax's label without requiring any mention of this risk." *Id.* at 1674 (emphasis added). Then, in 2008, after additional scientific evidence arose connecting Fosamax to atypical femoral fractures, the Court explained that Merck applied to the FDA for preapproval to change the drug's label, attempting to add language to both the Adverse Reactions and the Precautions sections of the label. *Id.* The Court emphasized that although the FDA denied Merck's request, it also invited the manufacturer to "resubmit" its application to "fully address all the deficiencies" identified by the FDA's review. *Id.* According to the Court, however, Merck "instead withdrew its application," choosing to make the changes to the Adverse Reactions section through the CBE process. *Id.* Moreover, with respect to the Fosamax label's eventual warning about atypical femoral fractures, the Court commented that Merck was "initially resistant" to the change, because it failed to reference "stress fractures." *Id.* at 1674-75.

in the first place. *Glossip v. Gross*, 576 U.S. 863, 882 (2015); *Exxon Co., U.S.A. v. Sofec, Inc.*, 517 U.S. 830, 841 (1996) (explaining that the Court "'cannot undertake to review concurrent findings of fact by two courts below in the absence of a very obvious and exceptional showing of error'") (quoting *Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 336 U.S. 271, 275 (1949)); *cf. Easley v. Cromartie*, 532 U.S. 234, 242 (2001) (doing so only when "there is no intermediate court," "we are the only court of review," "the trial here at issue was not lengthy and the key evidence consisted primarily of documents and expert testimony," and "[c]redibility evaluations played a minor role"). Saliently, Justice Alito concurred in part to ensure that the majority's "discussion . . . of the facts is not misleading." *Merck*, 139 S.Ct. at 1684. On this point, Justice Alito wrote, "[r]esolution of the legal question that the Court decides does not require much discussion of the facts, but . . . . the Court provides a one-sided account . . . [that] omits any mention of the extensive communication between Merck and the FDA during the relevant period." *Id.* at 1685. In the end, Plaintiffs' position cannot be reconciled with the Court's explicit decision to remand with instructions to apply its standards anew. *Cf. Farrar v. Hobby*, 506 U.S. 103 (1992) (deciding the merits rather than remanding); *McCkeskey v. Zant*, 499 U.S. 467 (1991) (same).

Plaintiffs then argue that the standard Judge Pisano applied in *Glynn* is somehow less demanding than *Merck*'s requirement that Defendant "fully" inform the FDA. Pl. Br., at 32-34 ("Judge Pisano did not apply the Supreme Court's standard [in *Merck*]."). But Plaintiffs never explain Judge Pisano's supposedly erroneous standard, the relevant difference between that standard and the *Merck* standard, or

why such a difference would be legally significant. Independently, I do not see any meaningful difference between what *Merck* demands and what Judge Pisano determined. Under *Merck*, the basic inquiry, which Judge Pisano applied, is whether the FDA had "all the information it deemed necessary to decide whether to approve or reject the proposed warning at the time it issued the [CRL]." *In re Avandia*, 945 F.3d at 759 (emphasis removed). Indeed, *Merck* itself phrases the inquiry in a substantially similar way: "the litigants may dispute whether the drug manufacturer submitted all material information to the FDA." 139 S.Ct. at 1680.

In any event, revisiting this question as a matter of first impression, as instructed by the Third Circuit, I reach the same result as Judge Pisano. Between its formal safety updates, periodic emails, and PAS, Defendant clearly and fully informed the FDA of the panoply of risks associated with long-term Fosamax use and the justifications for its proposed label change. Having culled through the extensive record, I summarize below what Defendant submitted to the FDA. Defendant repeatedly and voluntarily sent relevant articles to the FDA between 1992 and 2010. *See Fosamax*, 852 F.3d at 275 (citing A1774, A1258, A1237, A1243); Def. Rep. Br., Ex. 13, at A1928-33; *Fosamax*, 862 F.3d at 275 (further describing communications). Indeed, Defendant's 165-page March 2008 safety update, which surveyed medical studies, journal publications, and internal data compiled between July 16, 2007 and January 15, 2008, included numerous pages on atypical femoral fractures. Def. Rep. Br., Ex. 14. That safety update provided (1) an overview of three published safety studies identified in the medical literature describing new information regarding the

connection between prolonged alendronate[14] use and low-energy or atypical femoral fractures, (2) a discussion of eight publications on long-term therapy with bisphosphonates, including the link between prolonged bisphosphonate therapy and atypical low-energy femoral fractures, and (3) a summary of post-marketing data on atypical low-energy fractures associated with prolonged bisphosphonate therapy in response to the FDA's request for such an update. *Id.* at A2594-2613.

With respect to the three safety studies and various publications, Merck cautioned that although they contain important clinical information, some of the studies and publications found no "obvious defects in mineralization or bone quality after use of the drug." *Id.* at A2595. However, Merck did highlight one particular study that "raised the possibility of a link between prolonged bisphosphonate therapy and atypical low-energy non-vertebral fractures, predominantly with femoral diaphyseal location." *Id.* The authors of that study attributed this pattern of fractures to severely suppressed bone turnover that may develop during long-term alendronate therapy. *Id.* Similarly, several of the publications referenced in the safety update also hypothesized about a link between prolonged bisphosphonate therapy and the atypical low-energy fractures suffered by Plaintiffs. *Id.* at A2597-98. Finally, the safety update provided a trove of data, compiled from Merck's Worldwide Adverse Experience System database using search terms like "bone disorder," "stress fracture," "femur fracture," and "bone formation decreased." *Id.* at A2598-2613. Using these terms, Merck generated 175 post-marketing reports, providing insight

[14] Alendronate is a type of bisphosphonate.

into patients treated with alendronate sodium from October 1, 2005 through December 31, 2007. *Id.* at A2599. Specifically, the data from the post-marketing reports included, *inter alia*, the age and gender of the patient, location of the fracture, and the duration of alendronate therapy. *Id.* at A2609-10. While Merck commented that a review of the post-marketing reports did not provide "clear evidence of a causal link" between alendronate therapy and atypical low-energy femoral fractures, it committed to further monitor future reports for these types of fractures. *Id.* at A2613.

In June 2008, Defendant "promptly complied" with the FDA's request for further investigations that Merck had conducted and reports Merck had received. *Fosamax*, 862 F.3d at 275. And, what is more, Defendant's September 2008 PAS not only cited nine articles reporting cases of low-energy femoral fractures in Fosamax users, but included a clinical overview in which Defendant itself asserted a statistically significant association. *Cf. Wyeth*, 555 U.S. at 272-73 (noting that the manufacturer never "supplied the FDA with an evaluation or analysis concerning the specific dangers" at issue); *In re Taxotere (Docetaxel) Prod. Liab. Litig.*, No. 16-17039, 2020 WL 7480623, at *11 (E.D. La. Dec. 18, 2020) (finding that the FDA was not "fully informed" because its limited knowledge of the risk and repeated requests to the manufacturer for information indicated that the manufacturer was not "making an 'earnest attempt' to keep the FDA informed") (citations omitted). Despite this profuse evidence of information sent to the FDA, Plaintiffs, on remand, insist that more evidence was needed, and that Merck misled the FDA with the information it sent.

Having reviewed, myself, those documents, I find no basis in the record to reach that conclusion.

In that regard, Plaintiffs' evidence that the FDA was somehow left in the dark about the use of Fosamax and the potential risk of atypical femoral fractures is unpersuasive. Plaintiffs begin by offering six specific studies between 1995 and 2010 which purport to show a connection between long-term bisphosphonate use and atypical femoral fractures. The flagrant flaw with Plaintiffs' proffer, however, is that Defendant cited all these same studies in its communications with the FDA. Plaintiffs then take issue with minute details of the data Defendant submitted to the FDA, which they insist shows that Defendant "provid[ed] misleading information . . . [,] describ[ed] atypical femoral fractures inaccurately and conflat[ed] them with stress fractures." Pl. Br., at 31-32. Specifically, Plaintiffs maintain that Defendant (1) did not "provide the FDA with any possible pathogenesis for [atypical femoral fractures]," *id.*, Ex. 3, at A884; (2) stated in its clinical overview that "fractures with similar clinical features had previously been reported in patients not taking Fosamax," *id.* at A881; (3) "identified risk factors that simply were not associated with [atypical femoral fractures]," *id.*; and (4) failed to provide "additional information" after receiving the CRL in May 2009, "should have provided [the clarification which came from the September 2010 Task Force Report] much earlier," and "rebuffed the FDA's repeated pleas for further engagement" prior to the Task Force Report. Pl. Br., at 33-34. Based on the record before me, I disagree, and I address each of these, individually.

Pathogenesis. Plaintiffs first argue that Defendant did not provide the FDA with any possible pathogenesis, the manner of development of a disease, for atypical femoral fractures. The record belies this assertion. Defendant *repeatedly* indicated how Fosamax might cause the very injury Plaintiffs suffered. *See, e.g.*, Def. Br., Ex. 1, at A2757 (mentioning "[s]everely suppressed bone turnover"); *id.* at A2754 (describing "bone biopsy results" which "indicated low bone turnover"); Def. Rep. Br., Ex. 14, at A2597 (explaining, in its safety update, that the attached studies "related [atypical femoral fractures] to severely suppressed bone turnover that may develop during long-term" Fosamax use). In fact, in clinical trials three decades ago, Defendant informed the FDA that "antiresorptive agents may inhibit microdamage repair by preventing . . . bone resorption at the sites of microdamage," *Fosamax*, 852 F.3d at 275 (citing A1774), which was borne out to be the correct pathogenesis according to Plaintiffs' own experts. *Id.*, Ex. 3, at A880 ("[D]ecreased bone toughness can lead to stress fracture. Fosamax and other [bisphosphonates] can reduce the body's ability to repair a stress fracture once it has begun, prior to complete fracture. This might explain why a large number of bisphosphonate-induced stress fractures go on to completion."). Indeed, on appeal, the Third Circuit acknowledged that "Merck kept the FDA informed" of the "scores of case studies, reports, and articles … published documenting possible connections between long-term bisphosphonate use and atypical femoral fractures." *Fosamax*, 852 F.3d at 275. Plus, the FDA itself has since agreed that Merck "provided [the Agency] with the relevant scientific data about

Fosamax's risks." FDA Brief as *Amicus Curiae*, at *14.[15] Thus, based on the record, this argument lacks merit.

Clinical Features. Plaintiffs next argue that Defendant's clinical overview indicated that some clinical features associated with Fosamax use presented in patients not taking Fosamax. To be clear, the PAS stated, in this regard, only that "stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates." Based on this solitary statement, Plaintiffs suggest that by failing to communicate the "unique features" of atypical femoral fractures to the FDA, in particular, their "fracture pattern," Defendant created a misleading impression that such fractures are "much more common in the absence of [bisphosphonates]" than they actually are. Pl. Opp. Br., at 32.

Upon closer examination of the PAS's clinical overview, however, the Court does not find Defendant's submission misleading, deceptive, or ambiguous in any way. While the clinical overview identified that the fractures at issue here occur in a similar population of elderly individuals as other osteoporotic low-energy fractures, it also explained that "these [atypical femoral] fractures are less common than other osteoporotic low-energy fractures," and only represent "about 6% of fractures of the femur." In other words, Defendant informed the FDA that atypical femoral fractures are rare—even in elderly individuals who are taking Fosamax, and in that regard, there is no evidence in the record of Defendant "hiding-the-ball," as suggested by Plaintiffs. Moreover, while Plaintiffs take issue with the fact that the clinical

14 The Court notes that the FDA filed this brief as *amicus curiae* in support of Defendant in *Merck*.

overview states that atypical femoral fractures have been reported in patients not taking bisphosphonates, they fail to acknowledge the significant fact that the FDA-mandated warning *itself* observed that atypical femoral fractures occur in "osteoporotic patients who have not been treated with bisphosphonates." Indeed, all along, the FDA questioned whether taking bisphosphonates for a prolonged period of time would actually lead to more atypical femoral fractures because other osteoporotic patients, who were not on such therapy, also suffer from the same fractures. This is the very causation-related concern that led the FDA to reject Merck's PAS in the first place. *See infra*. In the end, even though the FDA approved an amendment regarding atypical femoral fractures, the warning includes the observation that osteoporotic patients, generally, have suffered such fractures. This fact, alone, dooms Plaintiffs' claim that Defendant misled the FDA by pointing out the same.

False Risk Factors. Plaintiffs contend further that Defendant emphasized "false risk factors" in materials sent to the FDA, the implication being that Merck "attempted to confound the true nature of the association between Fosamax and [atypical femoral fractures]." Pl. Br., at 32. Specifically, Plaintiffs argue that when the Task Force examined the actual data, some of the risk factors identified in the clinical overview and Defendant's proposed warning, namely, "abnormally decreased bone mineral density associated with osteoporosis, long-term immobilization/disuse, and use of glucocorticoids, the presence of joint deformity, leg-length discrepancies, muscle weakness, and spasm with resulting alteration in force distribution across the

joints," "simply were not associated with [atypical femoral fractures]." *Id.*, Ex. 3, at A882-83.

But, Plaintiffs misconstrue the language of the PAS to support their position. Rather, the "Spontaneous Reports" section of the clinical overview examined 132 reports where alendronate therapy was given for treatment of several conditions, looking specifically for evidence and information related to fractures. In part, it also discussed fracture risk factors, noting that 70 of the 132 reports provided sufficient information on the patient's medical history, concurrent conditions, and concomitant medications. In that regard, however, the clinical overview did not express any conclusions, nor did it make any pronouncements. Instead, it provided a laundry list of pre-existing conditions, comorbidities, and other attributes, along with the percentage of the 70 patients whose medical history reported those conditions. Specifically, the clinical overview stated that musculoskeletal disorders, including osteoarthritis and rheumatoid arthritis, were reported in 38 of the 70 patients; the "presence of joint deformities, muscle imbalance, leg-length discrepancies, and change in activity" were "common" for this subgroup of patients; and 28 of the 70 patients had a history of fracture. Indeed, the clinical overview also highlighted that only 10 of the 70 patients sustained atypical fractures following joint replacement or surgery, 17 patients had endocrine or metabolic disorders like diabetes mellitus and obesity, 10 patients reported malignant disease, and 3 patients were smokers. Thus, the purpose of the "Spontaneous Reports" section of the clinical overview was not to provide a definitive list of risk factors, but rather to provide a complete picture of the

clinical landscape to physicians prescribing Fosamax. Def. Br., Ex. 1, A2754-A2756. It was not meant, as Plaintiffs have advanced, to obfuscate the seriousness of potential injuries or to mislead the FDA. The record reflects that Defendant clearly appreciated the seriousness, and sought to alert the FDA, of these fractures on numerous occasions. *Id.* at A2756 ("[C]onsidering the clinical importance of these fractures . . . it is important to include an appropriate statement about them."). More compelling, the Task Force Report also concluded that certain fracture risk factors, unrelated to bisphosphonate use, exist; the Report specified that comorbid conditions are "Minor Features" of atypical femoral fractures, making them *relevant* rather than irrelevant. *See infra.*

Failure to Provide Additional Information. Finally, Plaintiffs assert that Defendant deprived the FDA of relevant information between 2008 and 2009, such as information that the Task Force eventually reported, leaving the agency "uncertain about the nature of atypical femoral fractures" and "[d]elayed by [Defendant's] inaction." Pl. Opp. Br., at 34. This argument also lacks merit. For one, Plaintiffs do not point to any specific instance in which Defendant failed to provide any timely and relevant information, data, case studies, or evidence to the FDA, or rebuffed a request for further engagement. While Plaintiffs make much of Defendant's decision to withdraw its PAS instead of applying for a formal meeting, they ignore the fact that Defendant did so at the FDA's direction, Def. Br., Ex. 3, at A1498, that it was entitled to do so by statute, 21 U.S.C. § 314.70(c)(6)(iii)(A), and that it subsequently stated in its CBE amendment to the Adverse Reactions section

that it *still* wished to discuss a Precautions warning. *Id.*, Ex. 4, A2963-64 ("Merck believes that further discussion with regard to text for the Precautions section of the label . . . would be beneficial."). Likewise, Plaintiffs' contention that, Defendant should have provided the additional information contained in the Task Force Report before the Task Force independently reviewed it, fails. The Task Force relied on 24 new case studies and 63 new articles *after* the FDA issued its CRL, according to Plaintiffs' own experts. Pl. Br., Ex. 3, at A879 ("In 2008 [at the time of the PAS], 13 of [ ] 37 published case series and reports [cited by the Task Force] were available to Merck. By May of 2009, 19 of [ ] 37 published case series were available to Merck. Additionally, the Task Force cited a total of 177 published or available articles and posters. Of those 177, 114 were available in 2008 [at the time of the PAS] or earlier and 120 were available before May of 2009."). Additionally, Defendant knew that the FDA, outside experts, and other manufacturers were working "closely" during this period to study atypical femoral fractures, which obviated the need to continue forwarding piecemeal research, *see, e.g.*, Pl. Br., Ex. 18, at A1508, particularly since the FDA specifically informed Merck that the Agency will continue to independently study and investigate the issues.

If any doubt remains as to whether Defendant fully informed the FDA of the justification for its warning, the Agency itself agrees that Defendant "provided [it] with the relevant scientific data about Fosamax's risks." FDA Brief as *Amicus Curiae*, at *14. Because the FDA alone is the "arbiter of which data and information is or is not 'material' to [its] decision to approve or reject a change to a drug's label" under

Merck, the FDA's view of the evidence matters.[16] *In re Avandia*, 945 F.3d at 759. Accordingly, I conclude that Defendant has satisfied the first *Merck* prong.

C. Prong 2 of Impossibility Preemption

As to the second prong of preemption, the crux of the parties' dispute is whether the FDA informed Defendant that it would not approve changing Fosamax's label to add the warning required by state law. Arguing in the negative, Plaintiffs advance two reasons why: (1) the CRL does not carry preemptive effective because it is not a final agency action, and (2) the FDA rejected Defendant's proposed warning for emphasizing "garden variety" stress fractures, not because it disagreed with the underlying science linking Fosamax use to atypical femoral fractures; in that regard, Plaintiffs claim that the Agency might have approved some other version of the warning had Defendant proposed one. I will address each, in turn.

i. The Preemptive Effect of the CRL

Plaintiffs argue—for the very first time in this long-pending MDL—that the CRL is not preemptive because it is not a final agency action which consummates the FDA's decisionmaking process. Pl. Br., at 12-14.

The Supremacy Clause grants "supreme" status only to the "the Laws of the United States." U.S. CONST. ART. VI, CL. 2. "Nothing short of federal law can have that effect." *Fellner*, 539 F.3d at 243; *Gibbons v. Ogden*, 22 U.S. 1 (1824). Federal agency actions can constitute "Laws" in the sense of the Supremacy Clause. *Hillsborough*

16 Because I conclude that Defendant fully informed the FDA of the justifications for its warning, I need not address Defendant's contention that Plaintiffs "waived any contrary argument [on this issue] several times over" by not raising it on appeal. Def. Br., at 20.

County, 471 U.S. at 713 ("[S]tate laws can be preempted by federal regulations as well as by federal statutes."); *New York v. Fed. Commc'n Comm'n*, 486 U.S. 57, 63 (1988) ("The phrase 'Laws of the United States' [in the Supremacy Clause] encompasses both federal statutes themselves and federal regulations that are properly adopted in accordance with statutory authorization"). However, this applies "only when [ ] [the agency] is acting within the scope of its congressionally delegated authority, . . . for an agency literally has no power to act, let alone pre-empt the validly enacted legislation of a sovereign State, unless and until Congress confers power upon it." *New York v. FERC*, 535 U.S. 1, 18 (2002) (quotations and alterations omitted); *Fidelity Fed. Savings and Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153-54 (1982).

Relying on Justice Thomas' concurrence, Plaintiffs argue that the CRL does not carry preemptive effect because it is not a final agency action. Pl. Br., at 27-28. According to Plaintiffs, the CRL does not mark "the consummation of the agency's decisionmaking process," *Bennett v. Spear*, 520 U.S. 154, 178 (1997) (quotations omitted), finally determine the parties' "rights or obligations," or impose "legal consequences." *Port of Boston Marine Terminal Assn. v. Rederiaktiebolaget Transatlantic*, 400 U.S. 62, 71 (1970). This argument is misplaced for several reasons. To begin, the majority in *Merck* explicitly cited 21 C.F.R. § 314.110(a), which empowers the FDA to "formally reject" a drug manufacturer's proposed warning through a CRL, as an example of an FDA action that *does* constitute "Law" in the sense of the Supremacy Clause. 139 S.Ct. at 1679. That should end the inquiry.

In any event, Plaintiffs' position appears to confuse the question whether an agency action is final—for example, for the purposes of providing judicial review under the Administrative Procedures Act, *Port of Boston*, 400 U.S. at 71—with the question of whether the agency action is "Law" with the power to preempt. These are distinct inquiries and have different legal consequences. The preemption question turns on whether Congress delegated to the agency the authority to act in such a manner in the first instance, not on whether the agency's action is necessarily a "final" one. *FERC*, 535 U.S. at 19 ("This sort of case . . . defining the proper scope of federal power . . . requires us to be certain that Congress has conferred the authority."). The yardstick is congressional intent, not the finality of its action. *See, e.g.*, *English v. General Elec. Co.*, 496 U.S. 72, 78-79 (1990) ("[P]reemption fundamentally is a question of congressional intent."); *Medtronic*, 518 U.S. at 485 ("'The purpose of Congress is the ultimate touchstone' in every preemption case.") (quoting *Retail Clerks v. Schermerhorn*, 375 U.S. 96, 103 (1963)); *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516, 530 n.27 (1992) (holding that the scope of preemption must rest "on a fair understanding of congressional purpose"); *Malone v. White Motor Corp.*, 435 U.S. 497, 504 (1978) ("It is uncontested that whether [the statute at issue is preempted] depends on the intent of Congress."); *Louisiana Pub. Serv. Comm'n v. FCC*, 476 U.S. 355, 374 (1986) (stating that the best way to determine preemption "is to examine the nature and scope of the authority granted by Congress to the agency").

It follows that for preemption purposes, it is mostly irrelevant whether the CRL is "of a merely tentative or interlocutory nature," *Bennett*, 520 U.S. at 178, or

that it simply "informs sponsors of changes that must be made before an application can be approved, with no implication as to the ultimate approvability of the application." 73 Fed. Reg. 39588. As Defendant points out, Def. Rep. Br., at 11-12, if Plaintiffs' position were to prevail, no CRL could ever carry preemptive effect because all CRLs require some subsequent action on the part of the manufacturer, and preserve some procedural mechanism to further engage with the FDA, even if futile. 21 C.F.R. § 314.110(b) (providing three options: "[r]esubmit the application . . . , addressing all deficiencies identified in the [CRL]," "[w]ithdraw the application . . . without prejudice to a subsequent submission," or "[a]sk the agency to provide . . . an opportunity for a hearing," after which "the agency will either approve" or "refuse . . . the application"). And, more importantly, it would abrogate the very preemption effect of the federal regulation, 21 C.F.R. 314.110(a), that the FDA promulgated pursuant to congressional authority. For these reasons, I reject Plaintiffs' claim that the CRL does not have preemptive effect under the Supremacy Clause. I turn, next, to the content of the CRL.

ii. The CRL

The parties dispute how to construe the meaning, and impact, of the CRL, which centers on four issues: (1) whether Defendant proposed an adequate warning; (2) whether the contents of the CRL, alone, support the inference that the FDA rejected Defendant's warning based on the Agency's belief that the underlying science did not justify one; (3) if the CRL does not convey such an inference on its face, whether the CRL, when construed in addition to the FDA's other communications

from the same time period, support that inference; and (4) how the surrounding regulatory regime informs the CRL. Plaintiffs posit that Defendant's warning was inadequate under state law, and the FDA rejected it merely because of the general "stress fractures" language, which does not indicate whether a differently worded warning would have been accepted by the FDA. Defendant, on the other hand, maintains that it sought to warn of the very injury Plaintiffs suffered, and the CRL—construed either on its own or in light of the FDA's other communications—prohibited Merck from adding any and all warnings to the Fosamax label because the Agency seriously questioned, and therefore doubted, a causal connection between bisphosphonates and atypical femoral fractures.

1. Adequacy of Defendant's Proposed Warning

To show that the FDA rejected a warning that would have been adequate under state law, Defendant must first establish that it actually proposed such a warning, an implicit but critical step in the analysis. Plaintiffs insist that Defendant failed to do so, because Defendant merely proposed "garden variety" stress fractures in its language, rather than atypical femoral fractures, despite scientific evidence allegedly differentiating between the two. Pl. Br., at 1, 5, 16. Plaintiffs point to the text of the warning as support: "every sentence after the first sentence described . . . 'stress fractures'" not "atypical" fractures, *id.* at 17, the warning referenced "similar clinical features" in fractures in "patients not treated with bisphosphonates," and Defendant suggested evaluating patients for other "known causes and risk factors," in addition to bisphosphonate use.

Defendant responds that it "tried to warn of the precise low-energy fractures that Plaintiffs allegedly suffered." Def. Rep. Br., at 5. In its proposed warning, Defendant highlights that it emphasized the essential features of atypical femoral fractures even if it did not use the term "atypical." *Id.* Defendant also points to "the warning that the FDA mandated following the Task Force Report," which conveys similar information as Defendant's proposed one, *id.* at 8, and which Plaintiffs concede is adequate. Pl. Br., at 10. Finally, Defendant notes communications with the FDA characterizing the warning as pertaining to "atypical . . . fractures," Def. Br., Ex. 2, at A1500; Pl. Br., Ex. 10, at A1145, and expert testimony that it "approach[ed] the FDA with respect to [such] fractures." Def. Rep. Br., at 8; Def. Br., Ex. 3, at A1498; *id.*, Ex. 15, at 660.

As an initial matter, Plaintiffs raised this argument before Judge Pisano to no avail. *Glynn*, 951 F. Supp. 2d at 701 (rejecting position that "the FDA rejected the PAS because [Defendant] used the phrase 'stress fracture' instead of 'atypical' fracture, and the FDA would have approved an appropriately worded warning"). After hearing expert testimony from both parties on the relevant terminology, Judge Pisano found Defendant's warning to contain "the same language" that Plaintiffs contend state law requires. *Id.* at 703-04.

I reach the same result upon a fresh review of the record. To reiterate, Merck proposed adding the following language to the Precautions section:

> **Low-Energy Femoral Shaft Fracture**
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated

> patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.

Pl. Br., Ex. 38 at A1371. To begin, I refer to the science regarding bone resorption and formation. All bones, whether healthy or osteoporotic, can develop microscopic cracks—called stress fractures—from everyday activity. These "ordinarily heal on their own through the bone remodeling process." *Merck*, 139 S.Ct. at 1673. When that process is disrupted, from a bisphosphonate for example, the body may not naturally repair itself, creating stress fractures as a result. Relevant here, stress fractures may then progress to atypical femoral fractures, or complete breaks of the femur, which cause pain and require surgery rather than rest. Stated differently, atypical femoral fractures *are* stress fractures, but more severe than other types of stress fractures, such as those that heal on their own. Shane et al., *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Second Report of a Task Force of the American Society for Bone and Mineral Research*, 29 J. Bone & Min. Res. 1, 12 (2014) (concluding same). Plaintiffs all but concede this point: atypical femoral fractures "start as . . . stress fractures." Pl. Br., Ex. 4, at 12.

It is also important to consider the Task Force Report, which defined key characteristics of, and risk factors for, atypical femoral fractures. The Task Force listed "Major Features," which are necessary to diagnose a patient with an atypical femoral fracture, and Minor Features, which may be associated with such a fracture but are not required characteristics. As to the Major Features, the fracture is (1) "located anywhere along the femur from the distal to the lesser trochanter to just proximal to the supracondylar flare"; (2) "associated with no trauma or minimal trauma"; (3) transverse or short oblique in configuration; (4) noncomminuted, meaning that there are not multiple breaks; and (5) complete in that it extends through both cortices and may be associated with a medial spike. The Minor Features are: (1) localized periosteal reaction of the lateral cortex; (2) generalized increase in cortical thickness of the diaphysis; (3) prodromal symptoms such as dull or aching pain in the groin or thigh; (4) bilateral fractures and symptoms; (5) delayed healing; (6) comorbid conditions (*e.g.*, vitamin D deficiency, rheumatoid arthritis, hypophosphatasia); and (7) use of pharmaceutical agents (*e.g.*, bisphosphonates, glucocorticoids, and proton pump inhibitors). Shane et al., *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral Research*, 25 J. Bone & Min. Res. 2267, 2268-69 (2010).

Having set forth the foundational science, I turn to the proposed warning. First, Plaintiffs argue that the title "Low-Energy Femoral Shaft Fracture" references "a broad category" of fractures including "[atypical femoral fractures] and less serious fractures," Pl. Br., at 17 n.3, and thus, does not constitute an adequate warning. I

disagree. The title itself describes aspects of an atypical fracture, that is, it occurs from minimal trauma (*i.e.*, low-energy) and in a discrete part of the thigh bone (*i.e.*, the femoral shaft), which, according to the Task Force, are the two Major Features of atypical femoral fractures. This is consistent with the Patient Packet Insert for Fosamax, which alerts patients that some users "have experienced fracture *in a specific part of the thigh bone*." Def. Br., Ex. 1, at A2742 (emphasis added). The first sentence of the warning then describes that the type of fracture at issue, or the subject of the warning, occurs in the "subtrochanteric and proximal" region of the "femoral shaft," which is another Major Feature identified in the Report, and a distinguishing characteristic according to Plaintiffs' own brief. Pl. Br., Add. 8 (containing an x-ray image of an atypical femoral fracture displaying these features); *id.*, Ex. 2, at A1148-49 (explaining that atypical femoral fractures are distinguishable, in part, because they occur "perpendicular to the femoral shaft" and in "the proximal (upper) third . . . or the subtrochanteric region").

Next, the warning advises that "[s]ome" low-energy femoral shaft fractures "[are] stress fractures." Plaintiffs interpret this sentence as conflating garden variety stress fractures with atypical femoral fractures, despite a distinction between them. Pl. Br., at 32 ("Merck improperly conflated the underlying fracture mechanism that leads to [atypical femoral fractures] with the ultimate outcome."). I do not see any basis in the science for such a strict dichotomy. As discussed *supra*, atypical femoral fractures *are* stress fractures, just severe ones and located in a particular part of the body, exhibiting a difference in degree but not necessarily in kind. *Merck*, 139 S.Ct.

at 1674 (stating that atypical femoral fractures "progress" from microscopic stress fractures); *Glynn*, 951 F. Supp. 3d at 704 (quoting one of Plaintiffs' experts who testified that Fosamax "can lead . . . to subsequent stress fracture formation"). In the Task Force's own words, "[t]he radiologic presentation of atypical femoral fractures bears striking similarities to that of stress fractures." Shane et al., at 2270. In addition, in Plaintiffs' expert's words, "decreased bone toughness can lead to stress fracture. Fosamax and other [bisphosphonates] can reduce the body's ability to repair a stress fracture once it has begun, prior to complete fracture. This might explain why a large number of bisphosphonate-induced stress fractures go on to completion." Pl. Br., Ex. 3, at A880.

On this point, Plaintiffs inexplicably overlook Defendant's PAS, which explains that Defendant uses the term "stress fracture" in its warning to mean an "insufficiency fracture" that occurs with no "identifiable external traumatic event." Def. Br., Ex. 1, at A2751-52. While the term "stress fracture" often, in generic terms, "connotes a fracture resulting from excessive loading of a normal bone," as is common in athletes, an "insufficiency [ ] fracture" is a specific *type* of stress fracture "caused by normal loading of poor-quality bone," as allegedly happened to Plaintiffs after taking Fosamax and about which Defendant sought to warn. DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 710-11 (29th ed. 2000) (defining an "insufficiency f[racture]" as "a stress fracture that occurs during normal stress on a bone of abnormally decreased density"). Defendant's PAS goes on to state that 91% of the fractures discussed therein, and referenced in the warning, resulted in surgical intervention, while the

other 9% involved patients who sustained only "incomplete stress fractures," Def. Br., Ex. 1, at A2755, which further distinguishes the warned-of injury from the garden variety type.

Next, Plaintiffs cite an internal email between Merck colleagues from December 19, 2010, in which several Merck employees shared redline revisions to rationales for their proposed changes to the Fosamax label. Pl. Br., Ex. 27, at A1573. Within those rationales, Defendant states that "most of the stress fractures general physicians have seen are associated with repetitive stress injury related to exercise (e.g., running) in younger adults, and that this type of stress fracture generally heals well with rest." *Id.* Plaintiffs offer this as "belated" evidence that Defendant knew its "proposed focus on stress fractures [in 2008] would confuse general physicians." Pl. Br., at 18. Having reviewed the email, such an inference cannot be drawn. Setting aside the questionable relevance of internal correspondence regarding the *FDA-mandated* label change over two years later, read in context of the email, Defendant's statement sought to *clear up* any confusion by suggesting that physicians *rule out* common causes before diagnosing a rarer atypical femoral fracture. Indeed, as the warning stated, because "[t]he number of reports of this condition is very low," patients should "be evaluated . . . for known causes and risk factors." This mirrors the Task Force's own determination two years later that atypical femoral fractures occur with "relative rarity" and may be "associated" with "comorbid conditions." Pl. Br., Ex. 2, at A1147.

Furthermore, Plaintiffs make much of the fact that atypical femoral fractures tend to "cause great pain," Pl. Br., at 5 (quoting *Merck*, 139 S.Ct. at 1674); *id.* at 6 (describing them as "debilitating"); *id.* at 17 (same, but "gruesome"), and they contrast this fracture with garden variety stress fractures, which usually heal themselves with rest and presumably do not cause much pain. *Id.* at 18. Plaintiffs argue that the lack of language regarding severe pain in Defendant's warning is evidence that Defendant was describing garden variety stress fractures. But Plaintiffs' position is belied by: (1) the Task Force's finding that such pain is a "Minor Feature," not a required characteristic; (2) Defendant's warning indeed provides that "[s]ome patients experience[] prodromal pain in the affected area" in any event, which suffices to capture any potential pain-related difference between atypical femoral fractures and garden variety stress fractures; and, most importantly, (3) the FDA-mandated label includes an almost identical statement, which Plaintiffs concede is adequate under state law. Def. Br., Ex. 7, at A1516-17. Further consistent with this purported feature of atypical femoral fractures, the Patient Package Insert instructs patients to "[c]all your doctor if you develop new or *unusual* pain in the hip or thigh." Def. Br., Ex. 1, at A2742 (emphasis added).

Relatedly, Plaintiffs emphasize the difference between "the nature" of garden variety stress fractures, which are "barely perceptible," and atypical femoral fractures, where "the thigh bone (the largest and strongest bone in the body) looks like a pencil snapped in two." Pl. Br., at 18; *compare id.*, Add. 8 (containing an x-ray image of an atypical femoral fracture), *with id.*, Add. 7 (containing an x-ray image of

a microscopic stress fracture). Again, however, Plaintiffs' argument that Defendant glossed over this unique feature of atypical femoral fractures in their warning lacks merit. Significantly, Defendant's warning explicitly describes "a complete fracture," a phrase that appears in the FDA-mandated label as well. The warning also cautions that such injuries can occur "weeks to months" after "prodromal pain . . . associated with imaging features of stress fracture." The term "prodromal" denotes a transitory phase between the appearance of an initial symptom—*i.e.*, a stress fracture—and the full development of a condition—*i.e.*, "a complete fracture" of the thigh bone. To that extent, the warning captures the progression from microscopic fracture to total shaft fracture that defines the relationship between bisphosphonates and atypical femoral fractures, and the impact Fosamax may have on this type of fracture overtime. *See* Pl. Br., at 32; *id.*, Ex. 3, at A880 ("Fosamax and other [bisphosphonates] can reduce the body's ability to repair a stress fracture once it has begun, prior to complete fracture.").

Additionally, Plaintiffs focus on another portion of Defendant's warning: "stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates," which "threaten[s] to mislead physicians [and the FDA] about the nature of the relevant risk." Pl. Br., at 18. As stated *supra*, I do not find this misleading, because the statement clarifies and underscores the rarity of atypical femoral fractures. In any case, according to the Task Force Report, the "nature of the relevant risk" *can* include comorbid conditions, which are a Minor Feature. Likewise, Plaintiffs offer nothing to reconcile their position with the fact

that the FDA-mandated warning contains precisely the same statement—"these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates." Def. Br., Ex. 7, at A1516-17. If the FDA warning is adequate, as Plaintiffs acknowledge, so must be the warning proposed by Defendant in this regard.

Finally, and more compellingly, regardless of any inadequacies in the text of Defendant's warning, the FDA clearly understood the type of fracture at issue. In a June 2008 email titled "Fosamax Information Request – Atypical Fractures," the Agency asked Defendant for more data concerning "the occurrence of atypical fractures." Pl. Br., Ex. 10, at A1145. Then, in an email from April 2009, the FDA described Defendant's PAS as the "currently pending [Supplemental Label Revision] for atypical fracture," and stated that it would likely approve "atypical fracture language" in the "postmarketing adverse events section of the label" only, Def. Br., Ex. 3, at A1498, which led to expert testimony at trial concluding that Defendant "approach[ed] the FDA with respect to atypical femur fractures" in 2008. Def. Br., Ex. 15, at T660:5-8. What is more, the FDA even called the fractures at issue "atypical" in its CRL, Def. Br., Ex. 2, at A1500; *id.*, Ex. 1, at A2751-52 (defining how the PAS uses the term stress fracture for the FDA, and distinguishing garden variety stress fractures), and stated in its October 2010 Safety Announcement that it had been studying "atypical" fractures all along.

Plaintiffs' only response to this evidence[17] can be distilled down to a single point: Defendant did not use the word "atypical" in its proposed warning. Not only is

[17] As discussed more fully, *infra*, this type of evidence, including email communications, may be considered by the Court in examining the CRL.

that a terse and superficial interpretation of the text, but as Judge Pisano observed, and I agree, "atypical" was hardly settled scientific jargon at the time. *Glynn*, 951 F. Supp. 3d at 704 (quoting one of Plaintiffs' trial experts who was "central" to their preemption argument, and who said that word was not "contrived" until about 2010). While this non-material characterization makes Defendant's warning different from the FDA-mandated warning, it does not make the warning any less adequate under state law, nor does it create the inference that Defendant misunderstood or miscommunicated the underlying science. To the contrary, Defendant's warning describes how/when atypical femoral fractures occur (low-energy events in the absence of trauma), where they occur (to the subtrochanteric and proximal femoral shaft), their nature (complete fractures), their progression (they develop out of garden variety stress fractures), and their severity (they can be associated with prodromal or unusual pain). Indeed, as explained *supra*, in this context, "atypical" is virtually synonymous with the term "low-energy" to describe the femoral fractures at issue. Accordingly, the warning had all the hallmarks of atypical femoral fracture such that not having employed the word "atypical" would not somehow change the nature of the proposed warning as plainly expressed by its language.

2. The Language of the CRL

Next, Plaintiffs argue that the CRL, by its terms, rejected Defendant's proposal based on language used, not on the fact that the FDA was unconvinced of a causal relationship between atypical femoral fractures and bisphosphonate. Pl. Br., at 19. Plaintiffs rely on the text of the letter to make this point, which, in Plaintiffs' view,

does not expressly reference any disagreement with the evidence linking atypical fractures to bisphosphonates. They also emphasize that Defendant's litigation position differs from its own scientists' "contemporaneous reading of the [CRL]." *Id.*, Ex. 29, at A1506; *id.*, Ex. 30, at A1504; *id.*, Ex. 17, at T265:12-18. Specifically, Plaintiffs point out that the day Defendant received the CRL, its Director of Clinical Research, Arthur Santora, interpreted it to convey that the "FDA wouldn't let [Merck] mention stress fractures." *Id.*, Ex. 29 at A1506. That same day, Plaintiff highlights that Defendant's U.S. Regulatory Liaison, James Adams, informed his colleagues that the FDA "believes that 'stress fractures' may not be clearly related to atypical subtrochanteric fractures." *Id.*, Ex. 30 at A1504. According to Plaintiffs, however, Adams later testified that the CRL does not mention any belief that "there was insufficient evidence to establish a causal association between Fosamax and atypical femur fractures." *Id.*, Ex. 17.

Defendant insists that FDA rejected its proposed warning in the CRL because "the data was not yet sufficient to allow for [such a warning]," rather than because the Agency disagreed with Defendant's wording. Def. Br., at 27. Like Plaintiffs, Defendant points to the text of the CRL, which states that the "justification" for the warning was "inadequate." Defendant reads this as "a commentary on the absence of a sufficiently clear link between Fosamax and the atypical fractures at issue." *Id.* And, because the CRL rejected Defendant's warning for "reasons," plural, the FDA could not have opposed the "stress fracture" language, alone. Def. Rep. Br., at 9.

The CRL was a response to Defendant's PAS, which, as discussed *supra*, sought to include a proposed warning that advised patients of the risk of developing atypical femoral fractures by taking Fosamax. In that regard, the CRL begins by describing Defendant's proposal as "adding language to the PRECAUTIONS section and the ADVERSE REACTIONS, Post-Marketing Experience subsection of the Package Inserts (Pls) *to describe low energy fractures at the* subtrochanteric region of the femoral shaft. In addition these supplements propose adding language describing this type of fracture in the Patient Package Insert (PPIs)." Def. Br., Ex. 2, at A1500 (emphasis added). The FDA rejected Defendant's proposal for amending the Precautions section, explaining:

> While the Division agrees that atypical and subtrochanteric fractures should be added to the ADVERSE REACTIONS, Post-Marketing Experience subsections of the FOSAMAX Tablets and Oral Solution and FOSAMAX Plus D Tablets labels, your justification for the proposed PRECAUTIONS section language is inadequate. *Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature.* Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting.

Id. at A1500-01 (emphasis added).

I appreciate that, as worded, the language of the CRL gives rise to competing inferences with respect to why the FDA rejected Defendant's warning. On the one hand, the CRL describes the "justification" for the warning as "inadequate." Logically, the CRL was presumably referencing the data Defendant submitted with its PAS, linking low-energy femur fractures to bisphosphonates. On the other hand, the CRL discusses Defendant's use of the term "stress fracture," stating that such fractures

"may not be clearly related to the atypical . . . fractures that have been reported in the literature" and it is "not warranted" to discuss risk factors for them. Def. Br., Ex. 2, at A1500-01. In light of these competing readings, I must look beyond the CRL's terms alone to ascertain its meaning and scope.

3. The FDA's Communications from the Same Time Period

If the CRL were the sum total of the evidence of FDA action in this case, Plaintiffs might be on firmer footing with regards to their preemption arguments. But, Defendant points to various communications from the FDA during the same time period to "understand what the FDA *action* [*i.e.*, CRL] meant." Def. Rep. Br., at 10. For instance, in April 2009, a month before the CRL, agency officials wrote that "the conflicting nature of the literature does not provide a clear path forward" on the question whether to add a warning to the Precautions section, Def. Br., at 26; Pl. Br., Ex. 33, at A1970-71, and "more time [would] be need[ed] for [the] FDA to formulate a formal opinion on the issue of a precaution around these data." Pl. Br., Ex. 12, at A1498; *id.*, Ex. 33, at A1970-71. As stated, *supra*, the data specifically involves atypical femoral fractures.

Then, in March 2010, the Agency stated that its review of the data "did not show an increase in th[e] risk" of atypical femoral fractures from bisphosphonate use. Def. Br., Ex. 5, A1508. FDA officials did not change their assessment until October 2010, a month after the Task Force issued its Report, *id.*, Ex. 10, at A1118-19; *id.*, Ex. 6, at A1392-93, which "clarif[ied] the features of atypical femoral fractures," Pl. Br., Ex. 20, at A1392, and "help[ed] the [Agency] understand [them] a little bit better."

Id. at A1396. But even then, the FDA did not observe a definitive causal link. Indeed, this series of events would not have occurred "if the agency already had a sufficient basis, in May 2009, to approve a warning" in the Precautions section. Def. Br., at 26. Neither would the FDA's own interpretation of the CRL in this litigation: it rejected Defendant's warning for "the lack of adequate data to support [it]," not "because of . . . the term 'stress fractures.'" FDA Brief as *Amicus Curiae*, at *31-32. Nevertheless, Plaintiffs argue that the FDA's informal email communications are not "Laws" in the sense of the Supremacy Clause, and in any event, Defendant "ignores the full context of what [the] FDA told [it]" at the time. Pl. Br., at 25.

Plaintiffs are correct that informal communications do not constitute "Laws" with the power to preempt. *In re Avandia*, 945 F.3d at 760 (holding that "an informal phone conversation with an FDA official is not an 'agency action taken pursuant to the FDA's congressionally delegated authority'") (quoting *Merck*, 139 S.Ct. at 1679). Yet, importantly, Defendant does not argue that the FDA's informal communications *themselves* establish preemption, only that they "shed light on" the meaning and scope of the CRL, which *is* "Law" with preemptive effect. Def. Br., at 30. I agree that it is appropriate to consider the communications for that limited purpose. *See, e.g.*, *Fosamax*, 852 F.3d at 293 (stating that the preemption inquiry involves an "evaluative inference about human behavior based on correspondence[] [and] agency statements"); Order at 1, No. 14-1900 (3d Cir. Nov. 25, 2019) (remanding to this Court "to determine the effect of the FDA's [CRL] and other communications"); Center for Drug Evaluation & Research, FDA, *CDER 21st Century Review Process: Desk*

Reference Guide 37 (2014) (explaining that the "[d]evelopment of final labeling" is "an iterative process between the applicant and FDA" involving significant correspondence); FDA, *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products* 21 (Apr. 2005) (addressing "communication between the FDA and applicants" during "labeling discussions"); 21 C.F.R. § 10.85(k) (providing that an FDA employee's written statement, which constitutes "an informal communication," "does not *necessarily* represent the formal position of FDA," a statement that by its terms contemplates that certain employee statements *may* do so); *In re Incretin*, 2021 WL 880316, at *16-17 (considered and credited such evidence); *Swanson v. Abbott Lab'ys*, No. 14-1052, 2017 WL 5903362, at *4 (S.D. Ohio Nov. 28, 2017) (same). Indeed, in Justice Alito's concurrence here, he suggested that informal communications between the FDA and drug manufacturers should be considered in the preemption analysis. *Merck*, 139 S.Ct. at 1685; *see In re Zofran (Ondansetron) Prods. Liab. Litig.*, 541 F. Supp. 3d 164, 194 (D. Mass. 2021).

Focusing on the sequence of communications and announcements from the same period, the CRL does not tell the whole story without the proper context gleaned from other FDA communications. The FDA received data regarding atypical femoral fractures long before 2008, and specifically sought more information in June 2008 on "atypical femoral subtrochanteric femur fractures," a request with which Defendant complied. Def. Br., Ex. 5, at A1508 ("All available case reports and clinical trial data were requested."); *Fosamax*, 852 F.3d at 296 ("It is undisputed that the FDA was

aware of the possible link between Fosamax and atypical fractures well before September 2010."). Defendant proposed amending both the Precautions and Adverse Reactions sections of the Fosamax label in September 2008, to include an appropriate warning about atypical femoral fractures, which was "important" to do given their clinical significance, even if it "was not possible with the present data" to establish causation, and even if the FDA was in the process of reviewing the issue. Pl. Br., Ex. 38, at A1349; Def. Br., Ex. 1, at A2756. The FDA rejected Defendant's Precautions warning in May 2009. In correspondence before sending the CRL, agency officials stated that the "conflicting nature of the [scientific] literature does not provide a clear path forward" on a Precautions warning, "more time [would] be need[ed] for [the] FDA to formulate a formal opinion on the issue of a precaution" based on the data, and Defendant's "elevation of [the warning] to a precaution" was "prolonging review."[18] Pl. Br., Ex. 33, at A1971. Then, after sending the CRL, the FDA expressed no desire to consider revisions despite Defendant's repeated inquiries to that end.

As late as March 2010, the FDA continued to believe that the "available" data "did not show an increase in th[e] risk" of atypical femoral fractures from bisphosphonate use, instructed doctors to "continue to follow" the existing Fosamax

18 As explained *supra*, the FDA clearly understood Defendant to be warning of the injury discussed in the literature, which is the same injury as Plaintiffs allegedly suffered. *See, e.g.*, Pl. Br., Ex. 10, at A1145 (asking Defendant for more data concerning "the occurrence of atypical fractures" in a June 2009 email titled "Fosamax Information Request – Atypical Fractures"); Def. Br., Ex. 3, at A1498 (describing Defendant's PAS as the "currently pending [Supplemental Label Revision] for atypical fracture" in an April 2009 email); Def. Br., Ex. 15, at T660:5-8 (Plaintiff's expert, Dr. Cheryl Blume, testified that Defendant "approach[ed] the FDA with respect to atypical femur fractures"); Def. Br., Ex. 2, at A1500 (calling the fractures at issue "atypical" in the CRL); Def. Br., Ex. 1, at A2752-52 (defining, for the FDA, how the PAS uses the term stress fracture).

label, and specifically noted a December 2008 study showing "similar numbers of atypical subtrochanteric femur fractures relative to classic osteoporosis" in patients not treated with bisphosphonates. The FDA made this Drug Safety Announcement pursuant to its Congressionally delegated authority. 21 U.S.C. § 355(r). The FDA also stated that it was "working closely with outside experts to gather additional information that may provide more insight." Def. Br., Ex. 5, at A1508. Construed in light of these various FDA communications, the CRL clearly rejected Defendant's warning, in part, because the FDA doubted the underlying science causally connecting bisphosphonate use and atypical femoral fractures.

It is also telling that, in the process of rejecting Defendant's Precautions warning, the FDA approved an Adverse Reactions warning for "low-energy femoral shaft and subtrochanteric fractures." The reason for the Agency's decision in this regard may very well be the different causal thresholds governing each section of the label. Indeed, the Precautions section requires "*reasonable evidence* of a causal association" to add a warning about an adverse event. 21 C.F.R. § 201.57(c)(6) (emphasis added). The Adverse Reactions section requires only "*some basis to believe* there is a causal relationship." 21 C.F.R. § 201.57(c)(7) (emphasis added).

Finally, the FDA, itself, believes that it rejected Defendant's warning for "the lack of adequate data to support [it]," and not "because of . . . the term 'stress fractures.'" FDA Brief as *Amicus Curiae*, at *31-32. Plaintiffs challenge this evidence because it is a "legal interpretation[] . . . submitted by government lawyers under a subsequent administration, nearly a decade after the fact," which represents the

views of the Office of the Solicitor General not the FDA. Pl. Br., at 22. I disagree on both points. First, "[I] have no reason to suspect that the Solicitor General's representation of [the FDA's] views reflects anything other than 'the agency's fair and considered judgment.'" *Geier*, 529 U.S. at 884. Second, an agency's fair and considered judgment as to the meaning of its own regulation and actions deserves some measure of deference. *Auer v. Robbins*, 519 U.S. 452, 461-62 (1997).

On the first point, it is appropriate to consider the FDA's views because Congress delegated to that agency the authority to implement federal drug regulations, it has expertise in that highly "technical" subject matter, and it is well-equipped to navigate "the relevant history and background" on such a "complex and extensive" issue. *Geier*, 529 U.S. at 883 (giving "some weight" to agency's view in a preemption case on similar grounds). Or, stated differently, the FDA is "likely to have a thorough understanding of its own regulation and objectives" with respect to any CRL it issues. *Id.*; *Medtronic*, 518 U.S. at 496 (relying, in part, on the FDA's interpretation of a provision's preemptive effect).

On the second point, I am not strictly foreclosed from crediting the FDA's reading of the CRL simply because the Agency advances it in litigation, particularly in light of all the other pertinent evidence. I am aware that in *Kisor v. White*, 139 S.Ct. 2400 (2019), the Supreme Court warned that "a court should decline to defer to a merely convenient litigation position or *post-hoc* rationalization advanced to defend past agency action against attack," such as a brand-new interpretation presented for the first time in legal briefs. *Id.* at 2417-18 (quotations and alterations omitted); *see*

also Christopher v. SmithKline Beecham Corp., 567 U.S. 142, 155 (2012); *Bowen v. Georgetown Univ. Hospital*, 488 U.S. 204, 213 (1988). But, *Kisor* sets forth "[t[he general rule," not an "entirely foreclosed . . . practice." *Kisor*, 139 S.Ct. at 2417 n.6. For example, the *Auer* Court deferred to a "new regulatory interpretation presented in an *amicus curiae* brief in [the Supreme Court]." *Id.* Where the agency is not a party to the litigation and has expressed its views only at the Court's invitation, as here, there is no reason to question whether it has provided its "fair and considered judgment" rather than an after-the-fact rationalization. *Id.* (citing *Auer*, 519 U.S. at 462).

In sum, when viewed in light the FDA's communications, the CRL rejected Defendant's Precautions warning because the FDA doubted the evidence linking bisphosphonate use to atypical femoral fractures in a causal sense. In other words, when it issued the CRL, the Agency believed that Fosamax's current label adequately reflected the results of the Agency's continuous and comprehensive evaluation of the risks associated with using Fosamax.

4. *The Regulatory Regime*

Finally, the parties use the regulatory regime, indeed some of the same provisions, to draw opposite inferences as to the meaning of the CRL. This is "highly relevant" and bears discussion. *Merck*, 139 S.Ct. at 1685 (Alito, J., concurring in the judgment) ("On remand, I assume that the Court of Appeals will consider the effect of [21 U.S.C. § 355(o)(4)(A)]."); *Seufert*, 187 F. Supp. 3d at 1175 ("[A] clear evidence

analysis must account for the regulatory framework governing prescription drug labeling.").

Plaintiffs argue that it is "dispositive" that the FDA "omi[tted]" any explicit discussion of the science linking bisphosphonates to atypical femoral fractures, because the agency must "describe all of the specific deficiencies that [it] has identified" when it sends a CRL. Pl. Br., at 20-21; 21 C.F.R. § 314.110(a)(1). To the extent that the FDA did not specifically raise causation as an issue, it cannot form any part of the basis for the agency's rejection, unless the agency "wrote a false [letter]." Pl. Br., at 20.

Defendant reads the regulations differently. Def. Br., at 25-27; Def. Rep. Br., at 11-12. According to Defendant, the FDA has a duty to mandate a label change if it "becomes aware of new information" that "should be included in the labeling." 21 U.S.C. § 355(o)(4)(A).[19] Defendant reasons that the FDA did not do so until October 2010, which implies that the FDA could not support a change before then and/or concluded that the Fosamax label conveyed the proper risk profile to the public at the time. Likewise, according to Defendant, the FDA will not reject a warning for "editorial" reasons, 21 C.F.R. § 314.105(b), and will "make every reasonable effort to communicate" any "easily correctable deficiencies" to a manufacturer "promptly," 21 C.F.R. § 314.102(b), including by suggesting remedies or recommending actions. 21 C.F.R. § 314.110(a). In light of these provisions, Defendant submits that based on the

19 Prior to October 2018, § 355(o)(4)(A)'s language contained slight differences not relevant here. *See* Substance Use-Disorder Prevention That Promotes Opioid Recovery and Treatment for Patients and Communities Act, Pub. L. 115-271, § 3041(b), 132 Stat. 3942-3943, effective Oct. 24, 2018.

FDA's statutory obligations, "[h]ad the Agency believed a [Precautions] change was justified earlier," or that the problem with Defendant's warning was fixable, such as Defendant's "stress fractures" language, "it would have taken [the necessary] steps," Def. Br., at 26, similar to the steps the FDA took as to Defendant's Adverse Reactions warning, Def. Br., Ex. 1, at A2732, and when Defendant, again, proposed stress fractures language in December 2010 in response to the Agency's mandated label.

First, while the CRL did not use certain terminology, which would have made it less ambiguous, this Court has found, *see supra*, that the CRL did in fact reject Defendant's proposed warning based on causation, and therefore, Plaintiff's argument in this context must be rejected out of hand. But, even if I were to accept Plaintiffs' position, one must assume that the FDA had reasonable evidence warranting a Precautions warning, but was so troubled by Defendant's use of the term "stress fracture" that it rejected a warning without offering any suggestions or revisions. To make such an assumption would effectively overlook the FDA's *raison d'etre* to regulate drug safety, its independent legal duty to notify a manufacturer as soon as it "becomes aware of new safety information that [it] believes should be included in the labeling of a drug" and "initiate discussions to reach an agreement . . . on labeling," 21 U.S.C. § 355(o)(4)(A), and the "presumption of regularity" accompanying its actions. Rather, "in the absence of clear evidence to the contrary, [FDA officials] have properly discharged their official duties." *United States v. Chemical Foundation, Inc.*, 272 U.S. 1, 14-15, (1926) (quoted in *Merck*, 139 S.Ct. at 1684 (Alito, J., concurring in part)). In other words, it is improbable that the FDA

declined to approve Defendant's Precautions warning, or failed to propose a solution to the problem it perceived with the language, *i.e.*, stress fracture, all while the FDA had sufficient causal evidence linking bisphosphonates to atypical femoral fractures and thus exposing patients to the risk of severe injury in the interim. *Accord Zofran*, 2021 WL 2209871, at *32 ("[T]he Court will not assume that the FDA failed to perform, in fact blatantly ignored, its statutory duties to review and monitor the drug for human safety . . . . Accepting plaintiffs' argument would suggest that the FDA . . . turned a blind eye to evidence that Zofran causes birth defects. That is highly unlikely, to say the least. And it is also unlikely . . . that it refused to take up the issue with Novartis based on the technical point that Novartis had not sought to change that specific section.").

The more likely scenario is that the FDA's *actions* taken in this case convey doubts that the Agency had about the underlying science, a deficiency *no* revision or edits could solve; hence, the Agency did not propose any. The FDA's subsequent *inaction*—it did not mandate a label change until October 2010, despite substantial ongoing review both internally and by the Task Force—confirms its then-existing perspective on the science, not that it was merely troubled by Defendant's phraseology of its proposed warning. *Ridinis v. Maurince*, No. 15-00020, 2020 WL 1264178, at *21 (W.D. Mo. Mar. 16, 2020) (holding that "continued inaction . . . in light of the known issues and the ongoing give-and-take between [a manufacturer] and the FDA" can constitute "clear evidence"); *In re Incretin-Based Therapies Prod. Liab. Litig.*, 142 F. Supp. 3d 1108, 1123-24 (S.D. Cal. 2015) ("The FDA's subsequent

inaction regarding drug labeling supports the conclusion that the FDA [did] not consider available scientific evidence of a causal association sufficient to warrant inclusion in the labeling . . . . [This] is highly persuasive given the FDA's comprehensive review of pancreatic safety and ability to mandate a label change."); *see also Merck*, 139 S.Ct. at 1685 (Alito, J., concurring in the judgment) (implying that FDA inactions in light of "[its § 355(o)(4)(A)] duty arguably affect the pre-emption analysis").

More to the point, the FDA "communicate[s] with applicants about scientific, medical, and procedural issues that arise" when it reviews a request for regulatory action. 21 C.F.R. § 314.102(a). More specifically, § 314.110(a)(2) imposes a "complete description" requirement when the agency sends a CRL; § 355(o)(4)(A) imposes an "obligation to initiate a label change" if the FDA believes one is warranted; § 314.110(a)(3) states that a CRL reflects the "FDA's complete review of the data submitted," not merely the particular labeling language proposed; and under § 314.105(b), the FDA may approve an application with "minor deficiencies" contingent on appropriate corrections. Taken together, these provisions warrant the following inference as to the FDA's intention when it issued the CRL: the Agency did not believe there was reasonable scientific evidence of a causal association between bisphosphonate use and atypical femoral fractures, or else it would have suggested edits to that end, or simply mandated a warning using language that the FDA thought was more appropriate, similar to what the Agency ultimately did in 2010.

What is more, the FDA red-lined Defendant's proposed "stress fractures" language between October 2010, when the Agency imposed a label change, and January 2011, when Defendant implemented the Agency's Precautions warning as-written. Were such language the sole problem with the 2008 warning, then the FDA could have simply stricken it, as it did two years later, or approved it on the condition that Defendant implement edits pursuant to 21 C.F.R. § 314.105(b). But, an issue existed in 2008 that did not exist in 2010, one that could not be resolved with any revisions: in 2008, the FDA was unconvinced of the causal link between bisphosphonate use and atypical femoral fractures. The Agency's contrasting approaches to Defendant's proposed "stress fractures" language cannot be reconciled otherwise. Accordingly, it follows from the regulatory regime that the FDA rejected Defendant's warning for lack of reasonable evidence of causation.

iii. The Scope of the CRL

Having determined the context of the CRL, I next determine the FDA's likely response to another proposed warning based on how it *did* respond in the CRL. *See, e.g.*, *Fosamax*, 852 F.3d at 293 (stating that the preemption inquiry requires "pars[ing]" the FDA's actual response "to discern what it suggests about the FDA's likely response"); *Dobbs v. Wyeth Pharmaceuticals*, 797 F. Supp. 2d 1264, 1277 (W.D. Ok. 2011) (finding preemption even though the FDA later determined that sufficient evidence existed to justify a warning, in part because it was "highly persuasive" that the FDA rejected a similar warning before).

1. A Revised PAS

Plaintiffs first argue that the FDA would have approved a differently worded Precautions warning had Defendant simply removed the "stress fractures" language and resubmitted its PAS. Pl. Br., at 29 ("FDA invited further action from [Defendant] on at least four occasions, over several months, in various formats (email, formal letter, telephone call). Thus, 'the ball was back in [Defendant's] court to submit a revised, corrected proposal.'") (quoting *Fosamax*, 852 F.3d at 299).

Judge Pisano disagreed, finding that "the FDA *would have* rejected a stronger Precautions warning because the FDA *did* reject a stronger Precautions warning" in the CRL. *OTSC Opinion*, 2014 WL 1266944, at *16. Construed in light of the FDA's communications and the regulations governing prescription drug labeling, I also find that: the CRL denied Defendant's Precautions warning because the FDA doubted the causal connection, if any, between bisphosphonates and low-energy femur fractures, and to that extent, the letter foreclosed the possibility that the FDA would have approved a differently worded warning in a revised PAS, without any substantial change in science.

Plaintiffs' evidence to the contrary is unavailing. Indeed, while the FDA mentioned working with Defendant in April 2009 "to decide on language" for a warning in the Precautions section, the Agency conditioned that response with explicit language that only "if it [was] warranted," an important qualification signaling the uncertain state of the underlying science. In fact, in the same email, the FDA instructed Defendant to "hold off" on a Precautions warning, which was

"prolonging review," so that it could "close out" its PAS and "agree quickly" to changes in the Adverse Reactions section, another sign that the Agency was not prepared to approve any revised Precautions language.

Plaintiffs also point to various interactions between May and July 2009, purporting to show that Defendant declined to engage with the FDA after the CRL was issued. Pl. Br., at 28-29. Each interaction, put into context, however, is an *attempt* by Defendant to *initiate* further discussion, which *the Agency* rebuffed. For instance, in a June 2009 phone call, Defendant asked for "a teleconference" to discuss revisions to its Precautions warning. Pl. Br., Ex. 13 ("I asked . . . would the Division be open to a teleconference to discuss what may be acceptable."). But the FDA responded that Defendant must "formally" request one. *Id.* ("[The FDA official] replied such requests should be made formally through a submission to the file.").

Soon thereafter, by email, Defendant reiterated its desire to discuss a Precautions warning. *Id.*, Ex. 14 ("Per your recommendation from a previous conversation this [potential] meeting would be requested formally as a Type C meeting."). Days later, however, the FDA informed Defendant in another phone call that it must "address *both* issues high-lighted in the [CRL] to initiate a new review cycle . . . or . . . withdraw the previous PAS." *Id.*, Ex. 15 (emphasis added); 21 C.F.R. § 314.110(b) (requiring a drug manufacturer to "address[] all deficiencies identified" by the FDA if it chooses to resubmit its application). One issue was the "inadequate justification" for the warning, which embodied the FDA's then-existing skepticism on

causation. Defendant received the same response when it asked the Agency to keep its PAS open pending further discussion.

Likewise, in its Adverse Reactions CBE amendment in July 2009, Defendant stated that it "still believe[d]" in a Precautions warning about "low-energy fracture[s]" and anticipated requesting a formal meeting on that issue per the FDA's prior instructions. *Id.*, Ex. 16. Defendant never did so, and Plaintiffs demand an adverse inference for it. But, Plaintiffs overlook the fact that withdrawal is a lawful response to a CRL. 21 U.S.C. § 314.70(c)(6)(iii)(A). Moreover, a formal meeting is not a prerequisite to preemption. *Dolin*, 901 F.3d at 814 (rejecting plaintiff's argument that defendant's failure to request a formal meeting with the FDA after receiving a CRL barred preemption, which "misunderstands the preemption standard"); *see also PLIVA*, 564 U.S. at 619-20 (rejecting plaintiff's argument that defendant's failure to ask the FDA to change the brand-name label barred preemption for a generic manufacturer, because what matters is that the manufacturer "cannot independently satisfy its state duties without the Federal Government's special permission and assistance").

Plaintiffs' argument is essentially that Defendant *could have*, *perhaps*, *theoretically*, changed the FDA's decision had Defendant somehow insisted on engaging with the Agency or invoked an available procedural mechanism rather than withdraw its PAS, but "the possibility of [that] possibility" is certainly not enough to "defeat[] pre-emption." *PLIVA*, 564 U.S. at 626 n.8; *cf. In re Actos (Pioglitazone) Prod. Liab. Litig.*, No. 11-2299, 2014 WL 4364832, at *20 (W.D. La. Sept. 2, 2014) (rejecting

manufacturer's preemption defense because of substantial evidence that the manufacturer declined various FDA efforts to require a stronger warning); *Dorsett v. Sandoz, Inc.*, 699 F. Supp. 2d 1142, 1159 (S.D. Cal. 2010) ("Defendants offer nothing but theoretical assumptions of what the FDA would have done, and that is not enough to warrant a finding of preemption."). Indeed, Plaintiffs have presented no evidence that the FDA made any suggestions, at the time it issued the CRL, that it would somehow change its decision regarding the proposed warning if Defendant made certain changes. Rather, the Agency rejected the warning based on a lack of scientific evidence, and it follows that the FDA would not have approved a Precautions warning had Defendant simply omitted the "stress fractures" language and resubmitted its PAS.

2. *A CBE Amendment*

Plaintiffs also suggest that Defendant, on its own initiative, could have amended the Precautions section of the Fosamax label through a CBE amendment. The CBE process permits a drug manufacturer to unilaterally add a Precautions warning to its label, but only if "newly acquired information" provides "reasonable evidence of a causal association of a clinically significant adverse reaction linked to a drug." 21 C.F.R. §§ 314.70(c)(6)(iii), 201.57(c)(6)(i). The question of whether newly acquired information exists is fact-intensive, but because it is "part and parcel of the broader legal [preemption] question," *Merck*, 139 S.Ct. at 1680, it is incumbent upon this Court to decide. *Lyons v. Boehringer Ingelheim Pharmaceuticals, Inc.*, 2020 WL 5835125, at *8 (N.D. Ga. Sept. 29, 2020) (collecting cases holding same).

"Newly acquired information" can take many forms. Information previously known to a manufacturer, but not submitted to the FDA, may suffice,73 Fed. Reg. at 49,606, as well as "data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) *if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA*." *Wyeth*, 555 U.S. at 569 (emphasis added); 21 C.F.R. § 314.3(b). This "accounts for the fact that risk information accumulates over time and that the same data may take on a different meaning in light of subsequent developments." *Wyeth*, 555 U.S. at 569. Notably, however, the CBE process does not exempt the proposed change from the FDA's substantive requirements, nor does it eliminate FDA jurisdiction—two points that Plaintiffs acknowledge. Indeed, the FDA retains authority to review amendments submitted through the CBE process, and it will reject a CBE amendment if, among other things, it concludes that there is insufficient evidence of a link between the drug and the adverse event or the proposed change "requires approval prior to distribution." 73 Fed. Reg. 2848, 2851; 21 C.F.R. 314.70(c)(5)(i); *see also id.* 314.70(c)(7) ("If the agency disapproves the [CBE], it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change."); 71 Fed. Reg. 3922, 3934 ("FDA reviews all such submissions and may later deny approval of" a CBE; "[t]hus, in practice, manufacturers typically consult with FDA prior to adding risk information to labeling"). Case law also highlights this important characteristic of the CBE process. *See Wyeth*, 555 U.S. at 571 ("Of course, the FDA retains authority

to reject labeling changes made pursuant to the CBE regulation in its review of the manufacturer's supplemental application, just as it retains such authority in reviewing all supplemental applications."); *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 392 (7th Cir. 2010) ("It is technically a violation of federal law to propose a CBE that is not based on reasonable evidence.").

Here, as of March 2010, the fact that the FDA still believed that "reasonable evidence of a causal association" was lacking and that it rejected Merck's proposed Precaution in 2009, demonstrate that it would not have approved the same change by way of a CBE amendment. *See Dobbs*, 797 F. Supp. 2d at 1276 (noting that the FDA had rejected risk information added by a CBE amendment because "it did not believe that a causal association" between the drug and the purported risk "has as yet been definitively established"). Indeed, as a matter of procedure, in order for Defendant to proceed with the CBE process after the FDA rejected its PAS—Merck was required to produce data indicating a greater-than-previously-known risk of atypical femoral fractures, which could establish "reasonable evidence" of a causal association. *Drescher v. Bracco Diagnostics, Inc.*, 2020 WL 699878, at *4 (D. Az. Jan. 31, 2020) (examining "whether Plaintiff has pled reasonable evidence of a causal association sufficient to allow a CBE label change"); *Dobbs*, 797 F. Supp. 2d at 1272 ("The FDA has consistently defined reasonable evidence . . . as 'when evidence exists on the basis of which experts qualified by scientific training and experience can reasonably conclude that the hazard is associated with the use of the drug.'"); 44 Fed. Reg. 2848, 2851 (allowing a CBE amendment only for "known hazards and not

theoretical possibility"); *id.* at 49,604 (stating that this is how the FDA ensures "scientifically accurate information appears in the approved labeling"); *see also Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699, 707 (2d Cir. 2019) (holding that manufacturers are "limited in their ability to unilaterally change the labels on their products" because they must comply with the CBE regulation's causation thresholds); *Merck*, 139 S.Ct. at 1677 (explaining that, "when the risks of a particular drug become *apparent*, the manufacturer has a duty to provide a warning that adequately describes the risk") (emphasis added).

Certainly, no additional data between the period of time when the FDA issued its CRL and when the Agency finally decided to issue a Precautions warning, "reveal[ed] risks of a different type or greater severity or frequency" than the ones which Defendant knew, informed the FDA, and sought to warn against in the first instance. 21 C.F.R. § 314.3(b). Defendant submitted its PAS in September 2008, concluding based on the research at the time that "[i]t is not possible with the present data to establish whether" Fosamax "increases the risk of . . . low-energy subtrochanteric and/or proximal shaft fractures." Pl. Br., Ex. 38, A1349. And, while Plaintiffs point to certain unidentified and unspecified case studies and articles, which purportedly demonstrate a different risk profile for Fosamax with respect to atypical femoral fractures that were available to Defendant between submission of its PAS in September 2008 and the Task Force Report in October 2010, those case studies and articles have neither been provided to the Court, nor summarized. Thus, the Court cannot evaluate the conclusions reached by those articles and case studies,

nor can it even definitively determine whether Merck ever independently reviewed or provided those materials to the FDA.

Moreover, even if those articles and case studies existed, in March 2010, the FDA announced that it had not seen "a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures," "an increase in the risk in women using [bisphosphonates]," or "[different] numbers of atypical subtrochanteric femur fractures" in "patients taking bisphosphonates" versus patients "not taking bisphosphonates" after reviewing case reports and clinical trial data from all bisphosphonate drug manufacturers. Pl. Br., Ex. 18, at A1508. These conclusions mirror those in Defendant's PAS, and to that extent, do not shed light on any "newly acquired information" in the sense of the CBE regulation. In other words, even though the FDA's then-ongoing review was arguably *more thorough* than any review it might have conducted under the CBE process—the Agency was compiling data from multiple manufacturers, analyzing a variety of new reports, revisiting old ones, conducting its own analyses, and working with outside experts on the Task Force—it did not uncover definitive evidence linking Fosamax use to atypical femoral fractures to a greater extent than Defendant originally indicated.

Then, in September 2010, the Task Force published its Report, which developed a "provisional case definition" for the "features for complete and incomplete atypical [femoral] fractures," reassessed prior studies in light of that definition, and reviewed a number of new articles/reports that Defendant had not previously submitted to the FDA, but added nothing not already known. Shane et al., at 2267-

69. Still, according to the Report, "a causal association between [bisphosphonates] and atypical fractures ha[d] not been established." *Id.* The science merely supported "evidence of a *relationship* between long-term [bisphosphonate] use and a specific type of subtrochanteric and femoral shaft fracture." Pl. Br., Ex. 2, at A1167 (emphasis added). Defendant and the FDA, alike, had long recognized the same. *See, e.g.*, Pl. Br., Ex. 10, at A1145 (stating, in June 2008, that the Agency was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates," that these were "reportedly rare in patients with osteoporosis not on bisphosphonates," and that it was "concerned about this developing safety signal"); *Fosamax*, 852 F.3d at 275 (citing A1258) (forwarding an article stating that Fosamax "may . . . potentially" increase the risk of such fractures); *id.* (citing A1237) (forwarding an article stating that Fosamax "may be associated" with such fractures"); *id.* (citing A1243) (forwarding an article stating that certain findings "raise[d] the possibility" that Fosamax may lead to such fractures).

Given the conclusions in the Task Force Report, there was no "newly acquired information" as defined in the CBE regulation on the basis of which Defendant could have successfully submitted a CBE amendment. *Accord In re Lipitor (Atorvastatin Calcium) Marketing, Sales Practices & Prod. Liab. Litig.*, 185 F. Supp. 3d 761, 769 (D.S.C. 2016) (holding that a drug label cannot be changed based solely on "information previously submitted to the FDA"); *Dolin*, 901 F.3d at 816 ("The [2011] article contained the same figures as GSK's 2006 analysis, which GSK submitted to the FDA. There is no basis to conclude that this was a new analysis or that it was 'not

previously submitted to the Agency.'"); *Knight*, 984 F.3d at 339 (explaining how a new article showing a "correlation" is insufficient to defeat preemption because the FDA already knew that); *In re Incretin*, 142 F. Supp. 3d at 1123 (stating that "indeterminate" or "inconclusive" evidence is not "reasonable evidence" sufficient to justify a CBE amendment); *Seufert*, 187 F. Supp. 3d at 1175 (stating that a CBE amendment "demands more than an indeterminate or inconclusive relationship"); *McGrath*, 393 F. Supp. 3d at 168 ("For the Court to draw the reasonable inference that Bayer could have unilaterally amended the Magnevist label in compliance with the FDA's CBE regulation, the Complaint must plead more than the mere possibility that Magnevist caused Plaintiff's fibrosis and related injuries."). The "new" evidence published after Defendant submitted its PAS, and relied upon by Plaintiffs, established the very relationship or connection Defendant had identified all along.[20]

The FDA responded to the Task Force by issuing another Drug Safety Announcement in September 2010, but with the same conclusion as before: the Report would "facilitate future studies" assessing a causal link between "these

20 The Task Force Report also "suggest[ed] that the risk rises with increasing duration of exposure." *Id.* But this was not new information to the FDA either. Pl. Br., Ex. 2, at A1147 ("The duration of [bisphosphonate use] relative to onset of the fracture was 5.3 years mean and 5 years median with a range from 3 months to 14 years."); *Merck*, 139 S.Ct. at 1674 (describing a report from a doctor in 2002 stating that his hospital called atypical femoral fractures the "Fosamax Fracture" because "100% of patients in his practice who have experienced femoral fractures . . . were taking Fosamax . . . *for over 5 years*") (emphasis added); *Merck*, 139 S.Ct. at 1674 ("[Defendant began receiving adverse event reports from the medical community indicating that *long-term Fosamax users* were suffering atypical femoral fractures.") (emphasis added); *Fosamax*, 852 F.3d at 275 (citing A1258, A1237, A1243) (describing how Defendant "began to see numerous scholarly articles and case studies documenting possible connections between *long-term Fosamax use* and atypical femoral fractures") (emphasis added).

unusual femur fractures" and bisphosphonate use, but "it is not clear if bisphosphonates are the cause [of such fractures]." Def. Br., Ex. 9, at A1512. This, too, echoes Defendant's original assessment of the science/evidence and implies no new risks or correlations of which the FDA was not already aware. *McGrath*, 2019 WL 2582530, at *5 ("Studies concluding it 'remains unknown whether GBCAs induce toxic effects' and that 'further studies are required to address possible clinical consequences of gadolinium deposition . . . in patients with normal renal function' do not constitute reasonable or well-grounded scientific evidence of 'clinically significant adverse effects' under the CBE regulation."); *Utts v. Bristol-Myers Squibb Co.*, 251 F. Supp. 3d 644, 669 (S.D.N.Y. 2017) (same, but with respect to articles that "merely express a desire for further investigation"), *aff'd sub nom. Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699 (2d Cir. 2019).

Finally, in October 2010, the FDA mandated a change to the Fosamax label, yet *again* it rejected any causal link, which is "squarely in line" with its prior conclusions and Defendant's ongoing dialogue with the Agency. *Lyons*, 491 F. Supp. 3d at 1364. The Task Force Report merely made the FDA "confident" that atypical femur fractures are "potentially more *closely related* to" long-term use of bisphosphonates "than [the Agency] previously had evidence for." Def. Br., Ex. 6, at A1392-93 (emphasis added). The now-current Fosamax label, as written by the FDA, refuses to go any further than Defendant's proposal thirteen years ago: "Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates." *Accord Matrixx Initiatives, Inc. v.*

Siracusano, 563 U.S. 27, 44 (2011) ("The fact that a user of a drug has suffered an adverse event, standing alone, does not mean that the drug caused that event.").

In any event, the FDA's review of Defendant's CBE amendment would not have been any less rigorous than its review of Defendant's PAS, particularly since the FDA was conducting its own review of causation at the time when Defendant had the opportunity to submit a CBE amendment, and Defendant's view of the scientific evidence would not have been entitled to extra (or any) deference. *Accord In re Incretin*, 142 F. Supp. 3d at 1125. In fact, drug manufacturers almost always consult with the FDA before submitting CBE amendments to avoid future enforcement action for an unwarranted warning. *Id.* There was much correspondence between the FDA and Defendant here, none of which indicated that the Agency would permit Defendant to implement a Precautions warning through the CBE process, but not through the PAS process. In fact, and importantly, the FDA suggested that Defendant submit a label change for the Adverse Reactions section through the CBE process, but it did not make the same recommendation for the Precautions warning. Based on these FDA communications, it is difficult to imagine that Defendant could have successfully changed the Fosamax label through the CBE regulation after the FDA rejected its PAS.

Contrary to Plaintiffs' position, while Defendant of course could have *tried* to submit a CBE amendment, regardless of futility, *Merck*, 139 S.Ct. at 1975; Pl. Br., Ex. 17, at T181:23-182:12, it need not do so merely to preserve its preemption defense. A manufacturer is under no obligation to use the CBE process to change the

Precautions section of its label for any reason other than reasonable evidence of a causal association. *Wyeth*, 555 U.S. at 571 (cautioning that the mere availability of a CBE amendment does not defeat preemption); *PLIVA*, 564 U.S. at 628 n.8 (noting that "the possibility of possibility" is not enough); *Dolin*, 951 F.3d at 890-91 (explaining how the phrase "would not have approved" in *Wyeth* implies that a drug manufacturer may prove preemption without showing that it ever attempted to make a label change); *Cerveny*, 783 Fed. App'x. at 804 n.8 (rejecting notion that "only labeling changes sought by the manufacturer can lead to preemption"); *Cerveny*, 155 F. Supp. 3d at 1213-16 (explaining that lower courts have "universally rejected" the notion "that [*Wyeth*] requires a showing that the manufacturer attempted to apply the warning suggested by the plaintiff but that the labeling was ultimately rejected by the FDA"); *In re Incretin*, 142 F. Supp. 3d at 1126 ("[*Wyeth*] does not require CBE submission and rejection."); *Zofran*, 2021 WL 2209871, at *32 ("Multiple courts have found preemption where the manufacturer had not requested the precise warning sought by the plaintiffs when the FDA had nonetheless made it clear that it would not accept that label change.").

A contrary rule would incentivize manufacturers to submit a CBE amendment regardless of risk magnitude or scientific justification, which would impose an undue burden on the FDA. *Wyeth*, 555 U.S. at 578-79 & n.11 ("[The] FDA has limited resources to monitor the 11,000 drugs on the market."); *Seufert*, 187 F. Supp. 3d at 1175 ("A rule to the contrary would encourage prophylactic labeling changes by manufacturers, which, in turn, could inundate the FDA with labeling submissions.");

FDA, *FDAAA Implementation – Highlights Two Years After Enactment* 7 (2010) (finding just 363 CBE amendments between 2009 and 2010). Not to mention that "[i]t is technically a violation of federal law to propose a CBE that is not based on reasonable evidence." *Mason*, 596 F.3d at 392; *Drescher*, 2020 WL 699878, at *4 (concluding same).

Moreover, the FDA does not approve CBE amendments simply out of an abundance of caution, as Plaintiffs seem to suggest. The Agency regulates drug labels for precisely the opposite reason: so as not to "cause meaningful risk information to lose its significance." 73 Fed. Reg. 2848, 2851 ("Exaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug . . . or decrease the usefulness and accessibility of important information by diluting or obscuring it."). Indeed, "[w]hile it is important for a manufacturer to warn of potential side effects, it is equally important that it not overwarn because overwarning can deter potentially beneficial uses of the drug by making it seem riskier than warranted and can dilute the effectiveness of valid warnings." *Mason*, 596 F.3d at 392. The FDA is thus appropriately wary of "the resulting information overload [which] would make label warnings worthless to consumers." *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 870-71 (7th Cir. 2010); *Muzichuck v. Forest Laboratories*, 2015 WL 235226, at *7 n.2 (N.D.W.V. Jan. 16, 2015) ("Public policy recognizes a danger in 'overwarning' consumers of potential drug-related risks."). Accordingly, Defendant could not have met the relevant CBE criteria had it

submitted a Precautions warning through that regulation after the FDA rejected its PAS.

CONCLUSION

Based on clear and convincing evidence, the Court finds that Defendant fully informed the FDA of the justifications for its proposed warning, which was adequate under state law and encompassed the injury Plaintiffs allege here. The FDA, in turn, informed Defendant that it would not approve changing the Fosamax label to include that warning in the CRL. Because the basis for the FDA's rejection was insufficient evidence of a causal link between Fosamax and atypical femoral fractures, the Court is satisfied that the evidence is clear and convincing that the Agency would not have approved a differently worded warning no matter how Defendant attempted to submit one. Plaintiffs' state law failure-to-warn claims are therefore preempted, and Defendant's Motion for Summary Judgment is **GRANTED**.

DATED: March 23, 2022

/s/ Freda L. Wolfson
Hon. Freda L. Wolfson
U.S. Chief District Judge